Diplomarbeit

THE ROLE OF OPTICAL COHERENCE TOMOGRAPHY IN THE DIAGNOSIS OF ERYTHEMATOSQUAMOUS SKIN LESIONS

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Graz, am 15.2.2016 *Clemens Cijan eh.*

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Zusammenfassung

Hintergrund

Aktinische Keratosen, Morbus Bowen, superfizielles Basaliom, Psoriasis vulgaris und nummuläres Ekzem können sich als erythematosquamöse Hautveränderungen präsentieren. Da die Behandlung dieser Krankheitsbilder deutlich variiert, muss zwischen ihnen verlässlich unterschieden werden können. Optische Kohärenztomographie (OCT) ist ein innovatives bildgebendes Verfahren, das zunehmend Verwendung in der Dermatologie findet. Der Stellenwert der OCT bei der Differentialdiagnose der zuvor erwähnten Hautveränderungen wurde noch nicht untersucht.

Ziel der Arbeit

Bezugnehmend auf den letzten Stand der Literatur wurden morphologische Kriterien für die optische Kohärenztomographie festgelegt, die den jeweiligen Krankheitsbildern zugehörig sind. In weiterer Folge wurde versucht, den Nutzen der optischen Kohärenztomographie bei der Differentialdiagnose von erythematosquamösen Hautveränderungen zu beurteilen.

Methode

Erythematosquamöse Hautveränderungen wurden mit HD-OCT abgebildet und auf das Vorhandensein von 30 definierten OCT Merkmalen untersucht. Mit statistischen Methoden wurden OCT Merkmale herausgefiltert, die bei der Differentialdiagnose erythematosquamöser Hautveränderungen hilfreich sein könnten.

Ergebnisse

Es wurden 51 Teilnehmer und Teilnehmerinnen mit 74 Läsionen eingeschlossen und von diesen insgesamt 220 High Definition (HD) OCT 3D-Bilder aufgenommen. Das durchschnittliche Alter der Studienkohorte (51% männlich, 49% weiblich) betrug 73 Jahre (±15,7 Jahre). Von den 74 inkludierten Läsionen war die Diagnose in 54 Fällen histologisch und in 20 Fällen klinisch gesichert.

Etablierte und häufige OCT-Merkmale wurden in Tabellen dargestellt und statistisch untersucht. Bei der Basaliom-Gruppe wurde ein Algorithmus von Boone et al. angewendet und evaluiert.
Außerdem wurde anhand der Ergebnisse der Studie ein Algorithmus zur Differentialdiagnose erythematosquamöser Plaques entwickelt.

Schlussfolgerungen

Die OCT ist ein geeignetes Verfahren zur Differenzierung der häufigsten Hautveränderungen, die sich als erythematosquamöse Plaques darstellen. Ein Zusammenhang zwischen bestimmten OCT-Merkmalen und Krankheitsbildern konnte ermittelt werden. Die Eignung des vorgeschlagenen Algorithmus bedarf weiterer Überprüfung.

Abstract

Background

Actinic keratosis, Bowen's disease, superficial basal cell carcinoma, psoriasis vulgaris and nummular eczema may present as erythematosquamous lesions. As their treatment varies significantly, an accurate differentiation between these entities is required. Optical coherence tomography (OCT) is an innovative optical imaging technology increasingly finding use in dermatology. The role of OCT for the differential diagnosis of the aforementioned diseases has not yet been explored.

Objective

With reference to current relevant literature (2015) we aimed to define morphological criteria identifiable in Optical Coherence Tomography of the respective diseases and tried to assess the value of Optical Coherence Tomography in the diagnosis of erythematosquamous skin lesions.

Method

Erythematosquamous lesions were imaged by HD-OCT and examined for the presence of 30 defined OCT features. Statistical analysis was performed to identify morphological findings possibly useful for the differential diagnosis of erythematosquamous skin lesions.

Results

Fifty-one participants presenting with 74 lesions depicted in 220 HD-OCT 3D images were included. The mean age of the study cohort (51% male, 49% female) was 73 years (±15,7 years). Out of the 74 included lesions, a histologically verified diagnosis was found in 54 cases and a distinct clinical diagnosis existed in 20 cases. The most common or established OCT features were presented and statistical analysis was performed. For the basal cell carcinoma group, an algorithm by Boone et al. was applied and evaluated. Finally, an algorithm for the differential diagnosis of erythematosquamous plaques was developed, based upon the results of the study.

Conclusion

OCT is a useful tool for differentiating common skin conditions presenting as erythematosquamous plaques. A correlation between certain OCT features and skin conditions could be confirmed. The eligibility of the proposed algorithm requires additional validation.

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List of Abbreviations

ACE	Angiotensin converting enzyme
AK	Actinic keratosis
BCC	Basal cell carcinoma
C5a	Complement component 5a
DEJ	Dermoepidermal junction
EGF	Epidermal Growth Factor
HD	High Definition
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HPV	Human papillomavirus
IFN γ	Interferon gamma
IL-2	Interleukin 2
IL-8	Interleukin 8
IL-17	Interleukin 17
LTB4	Leukotriene B4
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCT	Optical coherence tomography
PTCH/SMOH	Patched protein/ Smoothened receptor
Th1 cells	Type 1 helper T cells
TNF alpha	Tumor Necrosis Factor
TP53	Tumor protein p53

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INTRODUCTION

Optical Coherence Tomography in Dermatology

Historical aspects

Optical coherence tomography (OCT) is an innovative optical imaging technology. Comparable to sonography, it uses light instead of sound. OCT acquires cross sectional images of structures almost on a microscopic scale. Combined with other technical equipment, it provides *in situ* imaging in real time without the need to remove and process tissue samples, as essential in conventional histopathology (1). Originally a useful optical biomedical imaging technique, OCT has emerged to clinical medicine and has become a standard method in some medical fields. One of the main principles is low-coherence interferometry, which provides depth profiles of structures analogous to A-scans of the ultrasound imaging technologies (2). Originally used to measure the length of the eye, the A-scan method was developed at the University of Essen (3).

In 1990 the first B-scan method came up. Improvements of the latter method have been made by numerous institutions, such as the Department of Electrical Engineering and Computer Science at Massachusetts Institute of Technology (2). In 1993, again in the field of ophthalmology, the first *in vivo* medical image was published by Fercher et al (4). Gradually, OCT technology was introduced to many medical specialties, such as cardiology, gastroenterology, urology, surgery, neurology, pneumology and others.

OCT was used for the first time in dermatology in 1997 as a tool for clinical skin research. It is possible to distinguish epidermis and upper dermis. Skin appendages like sweat glands or hair follicles and blood vessels can also be depicted. OCT scanners specifically for dermatology have been designed for commercial sale and offer a promising tool in the field of skin research (2).

Technical aspects

While it is possible to directly measure reflected sound waves in sonography, this does not apply to light. With a velocity of around $3x10^8$ m/s and only short travelling distances in skin examinations, other solutions had to be found to measure the diminutive echo time delay of about 30 femtoseconds. Correlation and interferometry of low coherent light offer a key to solve this problem.
The Michelson type interferometer analyses backscattered light from the tissue sample by comparing it to the backscattered light of a known reference path length.
Initially, a source emits low-coherent or pulsed light, which is then split into two beams. One beam travels the known reference path and the other is directed to the tissue to be studied. Then the reflected light from both beams becomes united again. The resulting interference can be analysed and demodulated by the interferometer and axial image information is generated (1).
This axial image information can only be retrieved from infrequently scattered photons. Multiple scattered photons diminish the quality of the image. This circumstance can be resolved to some extent by filtering all photons travelling a longer distance than the reference path with a so-called coherence gate. Multiple scattered photons of shorter path length still downgrade resolution and contrast. Absorption of light plays a minor role in skin tissue (2).
Important parameters to take into consideration when using OCT are depth resolution and penetration depth (5). Penetration depth is depending on the wavelength of the light source, whereas larger wavelengths produce better images of deeper structures. Still, in first place wavelength has to be chosen in regards to the optical properties of the human skin to minimise absorption and scattering. This window of transmission lies between 700 and 1300 nm.
Another characteristic of the OCT is the independence of the lateral resolution from the depth resolution. As indicated earlier, the depth resolution is determined by the wavelength. However, the lateral resolution is determined by the spot size of the beam focus in the tissue (2). Resolutions of about 1µm have been achieved by special systems (6).

Another important parameter is contrast, which is created by the different refractive indices of the sample. Since scattering plays a crucial role in imaging quality, not the content of any pigment itself, but rather the density, distribution and orientation of the refracting media influence the contrast (2). The best contrast can be achieved with central wavelengths around 800nm (7).

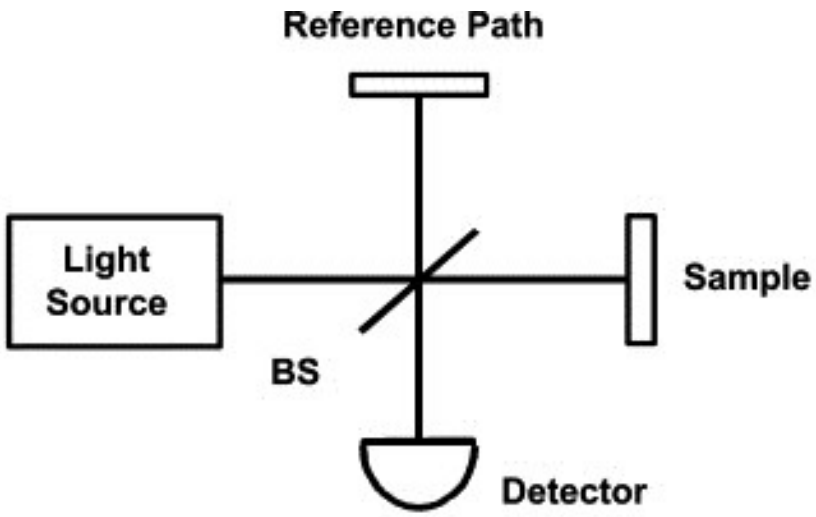


Fig. 1 Simplified illustration of the principle of the OCT.

Skin morphology in Optical Coherence Tomography

Morphology of normal skin

Epidermis

The first noticeable observation when examining the skin in slice mode (B-scan) is a highly reflective phenomenon on the skin surface, the entrance signal (8). The stratum corneum is best seen when examining palmoplantar skin, because only here it is thick enough for conventional OCT to be visualized. It presents as a well-demarcated, homogenous low-scattering zone and appears about 300 µm thick in OCT *in vivo* (2).

The next layers represent the rest of the epidermis. While scattering more intensely than the stratum corneum, it scatters lower than the dermis. It is possible to distinguish the dermoepidermal junction from the dermis as long as the margin is even. Also the basal layer and region around the basal membrane can be depicted and present as a weak signal adjacent to the papillary dermis.

Finally, the dermis appears brighter than the epidermis, with exception of possible blood and lymph vessels.
In addition to slice mode also the *en-face* mode can be used in OCT. When viewing OCT images in *en-face* mode, the stratum corneum presents again as the first layer. Due to its high refractive index, the keratin acts as a natural contrast agent and thus the margins of single corneocytes can be seen. The acaryote polygonal shaped corneocytes are arranged in groups separated by almost black skin folds.
The next layer is the stratum granulosum, which consists of two to four cell layers. The cells in this layer can be recognized by their dark centers, resembling the nucleus, which are surrounded by a bright and grainy cytoplasm.
Subsequently the stratum spinosum presents as a layer of smaller cells assembled in a tight honeycomb pattern.
Eventually the basal layer can be seen at the dermoepidermal junction, appearing as bright cells wrapping the dark dermal papillae.
These observations can only be made with High Definition (HD)-OCT (8).

Dermis

When viewing the dermis in *en face* mode, it presents as a bright zone due to its high collagen concentration, which leads to prominent reflection. Blood and lymph vessels can be identified.
Also deeper layers of the dermis can be visualized with OCT. It is possible to observe the superficial reticular dermis, which shows a web of reticulated fibres and small blood vessels. Pilo-sebaceus units are displayed as hollow-centred structures surrounded by elliptical cells with the hair shaft as a core (8).

Role of skin phototype

Since the melanin-rich keratinozytes of darkly pigmented skin tend to be more reflective, contrast is increased and differentiation of the specific skin layers is easier to achieve. Whereas for instance it may be difficult to delineate the basal layer in phototype II, it is more obvious in phototype V. Furthermore, the papillary dermis appears darker compared to the epidermis in higher phototypes (8).

Role of the anatomical site

Depending on the anatomical region, variants of skin architecture can be found. The most significant differences can be found between glabrous and non-glabrous skin. In palmoplantar skin a particularly bright band, corresponding to the entrance signal, can be distinguished.

Also, the stratum corneum is best seen on this site (8). The dermatoglyphics appear as a wavy pattern (2). Non-glabrous skin shows consistency to some degree. Reflectivity is influenced by the presence of skin appendages like hair follicles or sebaceous glands (8).

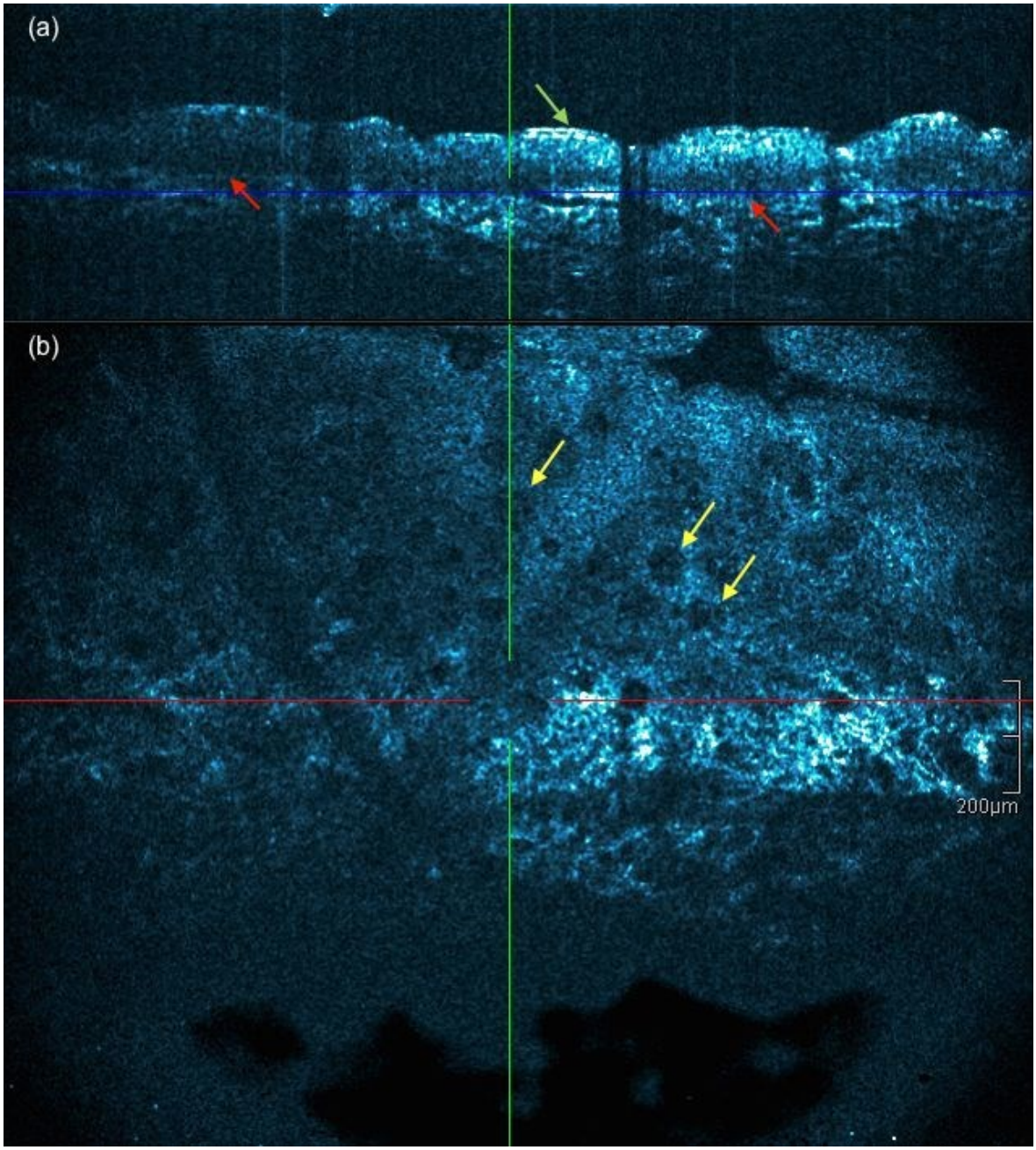


Fig. 2 Healthy skin. Cross-sectional (*a*) and *en-face* (*b*) view of healthy skin of the volar forearm. The stratum corneum appears as two bright lines separated by a thin dark line (*green arrow*) on the surface of the skin. The dermoepidermal junction (*red arrows*) is clearly distinguishable, with the darker lower layers of the epidermis bordering to bright fibrous structures and blood vessels of the upper dermis. In *en-face* mode, dermal papillae present as evenly distributed round and homogenously dark areas (*yellow arrows*).

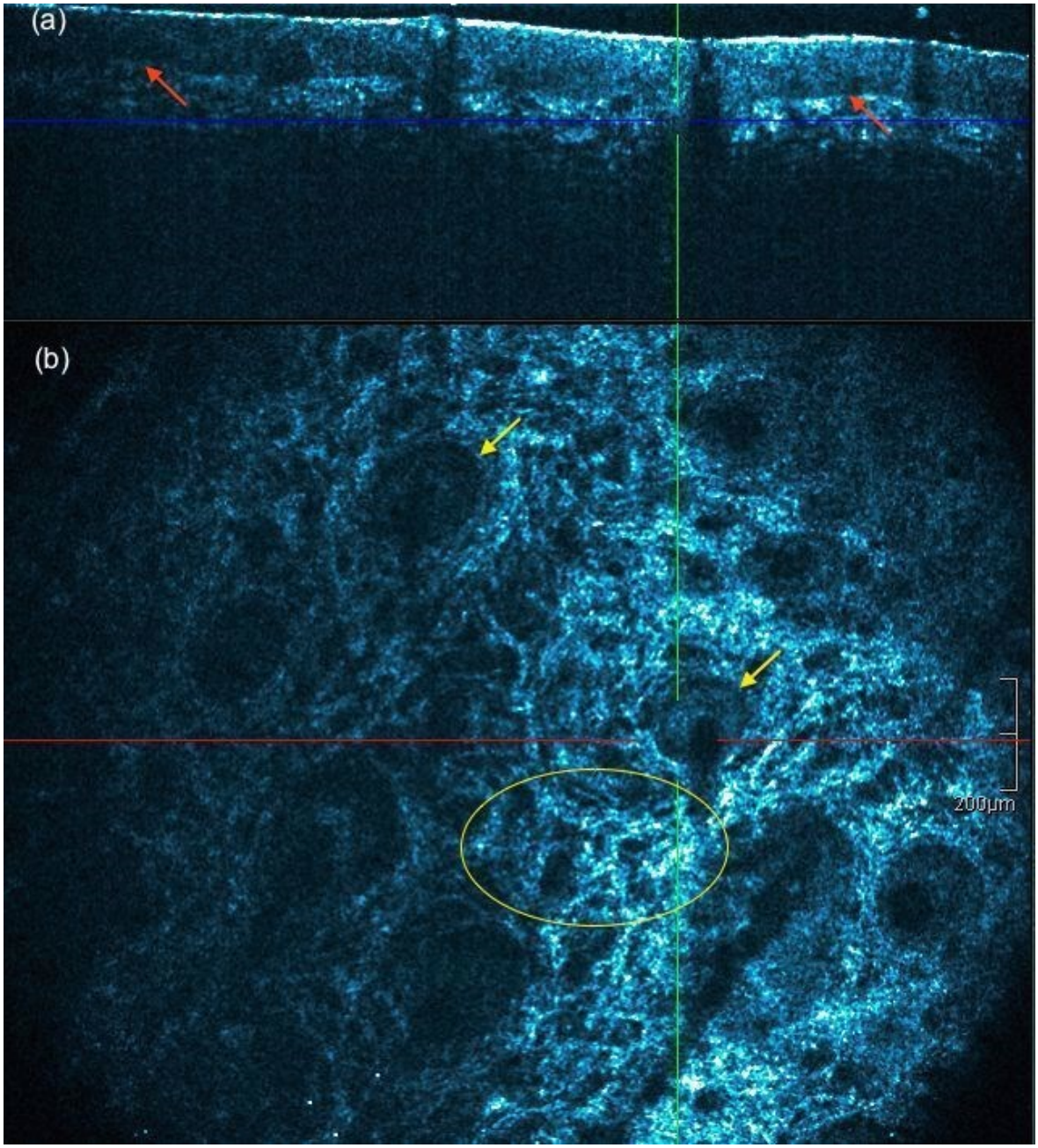


Fig. 3 Healthy skin. Cross-sectional (*a*) and *en-face* (*b*) view of healthy skin of the forehead. In *en-face* mode, hair follicles present as dark round structures with brighter content and often containing a hair shaft (*yellow arrows*). In cross-sectional mode they appear as lengthy structures and often significantly obliterate adjacent structures. Fibrous structures of the dermis appear bright and surround the dermal papillae and blood vessels (*yellow circle*). Again, the dermoepidermal junction (*red arrows*) is clearly distinguishable in cross-sectional mode, with the darker lower layers of the epidermis bordering to bright fibrous structures and blood vessels of the upper dermis.

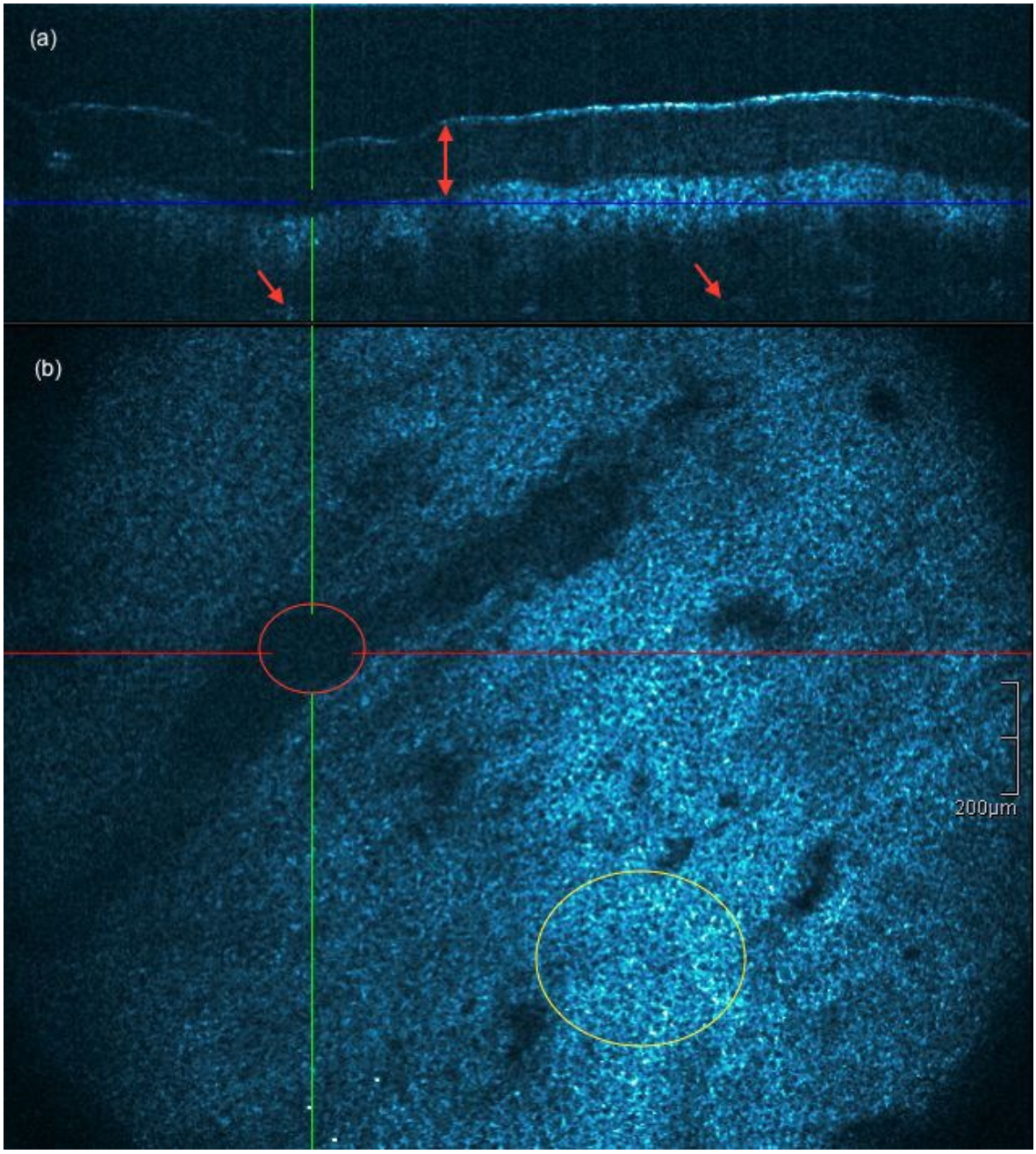


Fig. 4 Healthy skin. Cross-sectional (*a*) and *en-face* (*b*) view of healthy skin of the hand palm. The stratum corneum (*two-headed red arrow*), which is thicker than in other skin regions, presents as a dark region confined above and below by bright lines. The dermoepidermal junction (*red arrows*) is distinguishable in cross-sectional mode, with the darker lower layers of the epidermis bordering to bright fibrous structures and blood vessels of the upper dermis. Note that this characteristic is not as marked on the palm as in other skin regions. In *en-face* view, a regular honeycomb pattern is clearly visible (*yellow circle*). Due to the natural relief of the skin surface, different layers of the skin are visible in one slice. Fragments of the stratum corneum (*red circle*) projecting in the basal epidermis (*yellow circle*) can be seen in this image (*b*).

Morphology of pathological skin

Here a brief summary of phenomena, which can be observed in pathological skin conditions, will be given. Features associated with specific diseases will be discussed in detail in the respective chapters.

Alterations of epidermal and dermal architecture

Acanthosis can be identified as a thickening of the stratum spinosum or of the epidermis in general. Right beneath the bright entrance signal, a broadened dark zone indicates thickening of the stratum corneum and thus hyperkeratosis. The latter is often accompanied by parakeratosis, which presents as bright dots in the stratum corneum. Papillomatosis can be seen in *en face* mode at the dermoepidermal junction as numerous thickened rings (9). Irregularities of the size, shape and reflectivity of the keratinocytes can be summarized as atypical honeycomb pattern. Atrophy can be defined as an epidermis thinner than 40 µm and hypertrophy as an epidermis thicker than 60 µm (10).

Tumorous and cystic structures

Tumorous structures present as homogenous grey structures, often surrounded by a peripheral rim. Various features might be noticed alongside the presence of tumorous structures. Fibrous structures appear to be stretched and dark streaks emerge into the epidermis. Also, increased vascularization can be seen (11).

Signs of inflammation

Inflammatory reactions in the skin sometimes cause spongiosis or acantholysis. Spongiosis is observed as broadened intercellular space between the keratinozytes, which appears as a dark halo. Acantholysis presents as a dark rim in the epidermis, occasionally accompanied by necrotic and inflammatory cells. Eventually, blisters may form. These can be identified as dark round areas. Further, very bright dots corresponding to lymphocytes can be seen, often surrounding the significantly dilated blood vessels of the papillary dermis (9).

Skin conditions presenting as erythematosquamous plaque

Definition of erythematosquamous skin lesions

The term erythematous plaque refers to a broad spectrum of inflammatory, infectious and/or tumoral skin manifestations, which are all characterized by a slightly elevated red and scaly clinical appearance.
Depending on the underlying pathogenesis, lesions may present as single or multiple, well or poorly defined, large or small lesions with or without further associated morphological characteristics.
Common lesions presenting as erythematosquamous plaques are for example actinic keratosis, Bowen's disease and basal cell carcinoma, but also psoriasis and eczema, which will be further discussed in detail.
An erythema (from the Greek erythros, meaning red) is „ redness oft the skin or mucous membranes, caused by hyperemia of superficial capillaries" (12). A plaque is a flat topped, elevated primary lesion and usually defined as 1,0 cm or larger in diameter. It can originate from the epidermis as well as the dermis.
A scale, or squama, is a secondary lesion formed by a conglomerate of cornified epithelial cells (13).

Actinic keratosis

Epidemiology and pathogenesis

Actinic keratosis (AK) is one of the most common skin diseases of humankind in the world, preferably developing in fair skinned persons. Whereas it used to be more prevalent in men due to occupational UV-exposure, today's recreational habits lead to an equal incidence in women. In Europe and the USA almost 100% of the population of 70-year-olds are affected (13).

Pathogenetically, UV radiation promotes the development of actinic keratosis by damaging the keratinocytes' DNA as well as reducing the immunological response and disturbing DNA repair mechanisms. Impaired growth, proliferation and keratinization of the damaged cells follow. At some point the malignant cells may breach the epidermis and become an invasive squamous cell carcinoma. This occurs in an estimated 5 - 10% of actinic keratosis over the course of 10 – 20 years (13).

Morphology of actinic keratosis

Clinical features of actinic keratosis

Actinic keratoses typically develop on chronically sun-exposed body parts, such as the bald scalp, face and dorsum of the hands. Before becoming visually distinguishable, early lesions can be noticed by palpation as rough macules or patches. Later on they clinically present in various patterns, most commonly as scaly lesion with colours ranging from pink to dirty yellow or brown (13).

Histological features of actinic keratosis

In histopathologic analysis, the most significant feature is the occurrence of atypical keratinocytes, which do not infiltrate the dermis and are mostly observed in the stratum basale, representing the damage dealt to the level where proliferation happens.

Other findings correlate with the rich variety of the clinical appearance, typically involving parakeratosis interchanging with hyperkeratosis. Solar elastosis is always found to some extent in the dermis. Also, telangiectasia and an inflammatory infiltrate may occur, whereas hair follicles and gland ducts are often spared in early actinic keratosis.

Depending on the features there exist numerous histological subtypes. A histologic sample may be labelled as bowenoid actinic keratosis if atypia involves the entire epidermis. Particularly thick lesions show acanthosis, while thin lesions are atrophic. A confined hypertrophy of the stratum corneum may pose as cornu cutaneum accompanied by actinic keratosis. Variants with pigmentation present with an accumulation of melanin in the basal layer and papillary dermis (13).

The discrimination between actinic keratosis, Bowen disease and superficial basal cell carcinoma as well as lightly pigmented seborrheic dermatosis or verruca may be a differential diagnostic challenge, especially in single skin lesions (13).

OCT and actinic keratosis

When viewing actinic keratosis in OCT, hyperkeratosis and parakeratosis can be found. Zones with thickened epidermis, as well as with thinned epidermis occur. The dermoepidermal junction may be obscured. The honeycomb pattern, which can be identified in normal skin, is mildly to severely atypical (10). In early lesions, these irregularities seem to be restricted to the lower third of the epidermis. A perivascular inflammatory infiltrate can be seen(14). Hair follicles may be involved, presented by atypical keratinocytes restraining the follicle.
A hypertrophic and a lichenoid variant can be distinguished. OCT is a helpful tool when trying to discriminate actinic keratosis from squamous cell carcinoma. In squamous cell carcinoma, the dermoepidermal junction is obliterated or interrupted by hyporeflective buddings and the adnexal involvement is decisively more pronounced. The epidermal and dermal architecture is distinctly atypical and acantholysis can be observed (10).

Bowen's disease

Epidemiology and pathogenesis

Bowen's disease is a form of squamous cell carcinoma in situ, which affects mostly fair skinned people in their middle or old age (13). Bowen's disease can develop virtually at any body site, hence may be found also on non-UV-exposed skin. Although there are seemingly regional differences in sex incidence there is no conclusion on this subject. Historically, arsenic was associated with Bowen's disease (15). Particularly the occurrence of multiple tumors may be a hint for a carcinogenic cause. Also ionizing radiation can promote the development of Bowen's disease (13).

HPV may be another promotor, especially in anogenital and periungual lesions, further immunodeficient patients show a higher incidence of Bowen's disease. About 5% of the lesions become invasive and again circa 30% have the potential to form metastasis (15).

Morphology of Bowen's disease

Clinical features

Clinically Bowen's disease presents as a slowly expanding, persistent erythematous and scaly patch or plaque, akin to psoriasis or dermatitis. Very rarely pigmented variants can be found (15). Hence when trying to classify psoriasiform or dermatitis-like patches, which slowly grow and show no sign of regression under therapy, one should think of Bowen's disease, superficial basal cell carcinoma or perhaps extramammary Paget disease. On the other hand, early psoriasis or nummular dermatitis and also cutaneous lupus erythematodes may be misinterpreted as Bowen's disease, but will respond to therapy (13).

Histological features

Regarding histopathological features, Bowen's disease shows dysplasia in the whole epidermis, typically affecting also epidermal parts of the cutaneous adnexae. The large, abnormal keratinocytes have lost polarity and ignore epidermal architecture and produce an image with marked acanthosis and parakeratosis. Individual keratinized cells and frequent mitoses can be observed. There are signs of inflammation in the dermis with primarily T-lymphocytes and at times the vascularization is abnormal. Several histological subtypes can be identified, namely among others the psoriasiform, atrophic and verrucous hyperkeratotic form (15).

OCT and Bowen's disease

Only little focus has been put on OCT findings of Bowen's disease so far (October 2015). It appears that there are similarities with actinic keratosis and squamous cell carcinoma. Epidermal thickening and hyperkeratosis can be observed and the dermis is only poorly reflective (16).

Basal cell carcinoma

Epidemiology and pathogenesis

Basal cell carcinoma (BCC) is the most common malignant tumor in mankind with an increase in incidence of 3 to 8% a year. The skin types I and II have the highest risk of developing basal cell carcinoma. Mostly elderly people are affected and there is a significant preference of the male sex. Young patients who present with basal cell carcinoma should be examined for hereditary disorders like the nevoid basal cell carcinoma syndrome. There are also regional differences with a 20 times higher incidence in Australia than in England (13). In the United States basal cell carcinoma makes up about 30% of all cancers and is 20 times more frequent than melanoma and 4 to 5 times than squamous cell carcinoma. In 1994 the incidence for basal cell carcinoma was 407 out of 100,000 for men and 212 out of hundred thousand for women (15).

Genetic as well as environmental factors have been identified to play a role in the development of basal cell carcinoma. Ultraviolet radiation, especially UVB is known to cause typical mutations, which can be found in basal cell carcinoma. The latency period seems to be around 15 to 20 years (13).

Another factor is ionizing radiation, whereas multiple low intensity doses rather than a singular high dose lead to tumor growth. Further, carcinogens seem to be able to induce basal cell carcinomas, especially of the superficial type. Immunosuppressed patients have a reduced T cell response, which favours basal cell carcinoma development, as observed in patients with HIV/AIDS and hematopoietic malignancies. Also, chronically damaged skin offers ground for basal cell carcinoma to originate. Thus, it can be found on scars and pressure marks, chronic inflammatory dermatoses and persistent ulcers as in stasis dermatitis. On a molecular level two mutations can frequently be observed, namely mutations of PTCH/SMOH genes, which are involved in the sonic hedgehog pathway, and mutation of TP53. Basal cell carcinoma metastasizes in an estimated 0,003 to 0,1% (13).

Morphology of basal cell carcinoma

Clinical features

There are numerous clinical and histological variants of basal cell carcinoma, which play an important role in the differential diagnosis of many dermatoses. The initial basal cell carcinoma may present as a very subtle indurated pearly area with telangiectasia. An early basal cell carcinoma should be ruled out in any case of non-healing facial lesion.

The nodular basal cell carcinoma is the commonest subtype, showing pearly and waxy borders with prominent telangiectasia and occasionally a central depression or ulceration with a crust. The pigmented basal cell carcinoma may have clinical similarities with many other pigmented dermatoses and the cystic variant poses as a translucent bluish-white skin lesion.

Another variant, which needs a more aggressive therapy due to its invasiveness, is the morpheaform basal cell carcinoma. It usually presents as an elevated atrophic scar with telangiectasia and may be confused with morphea, an atrophic scar or a keloid.

The superficial or multicentric basal cell carcinoma presents as a differently looking subtype compared to other variants and hence is often misdiagnosed. Clinically typical findings are distinct erythematous, crusted patches or plaques with only subtle pearly papules and occasionally a decent zone of hypopigmentation on the margins. They often mimic the appearance of Bowen's disease or dermatitis or, if pigmented, of seborrhoic keratosis (13). Particularly multiple lesions may be confused with psoriasis (15). Most commonly they form on the trunk and sometimes cause pruritus (13).

Histological features

In histopathologic analysis, two cell populations can be distinguished. Firstly, basaloid cells and secondly, a fibrous stroma which surrounds them. It is assumed that the tumor derives from undifferentiated pluripotent epithelial cells and therefore tumor cells have a similar appearance as cells of the basal layer and hair follicle and also share numerous immunohistochemical and ultrastructural features with follicular matrix cells.

The fibrous stroma seems to be mandatory for the basaloid cells to thrive, supporting the theory of a mechanism resembling a damaged embryologic differentiation as a trigger for basal cell carcinoma (15). The tumor cells have a round to oval nucleus surrounded by little basophilic cytoplasm. They form nests with palisading in the periphery and are often separated from their fibrous stroma by a cleft in hematoxylin-eosin stain. The epidermis itself may show atrophy or ulceration. The histologic picture often shows similar features to the clinical picture and hence offers a corresponding variety (13). The superficial variant forms their basaloid lobules from the lower margin of the epidermis. The lobules, although seemingly isolated, are interconnected and may become invasive. Defining the borders is often difficult and therefore recurrences after excision tend to be common (15).

OCT and basal cell carcinoma

One of the main findings in OCT images of basal cell carcinomas is the presence of dark lobulated structures (11). These solid tumors have a homogenous greyscale distribution and seem to correlate with histological findings. Often the tumor mass, which is more reflective than the rest of the epidermis, is separated from the surrounding stroma by a thin hyporeflective zone (2). This cockade feature is preferably found in lobules connected with the epidermis (11). Tumor aggregates in the dermis tend to be rather hyporeflective. Compared to normal skin, irregularities in the epidermal and dermal architecture can be seen in affected tissue. Bright plug-like structures and extensive dark zones in the upper dermis can be identified (2). There are hints that also the subtypes of basal cell carcinoma could be discriminated with OCT. In particular, the combination of lobular structures adjacent to the epidermis and small epidermal projections into the dermis with intact dermoepidermal junction seem to appear only in superficial basal cell carcinomas. Further, no stretching effects could be detected in this subtype (11).

Psoriasis

Epidemiology and pathogenesis

Psoriasis is a chronic inflammatory disease of the skin. Its clinical appearance has an impressively wide range and numerous factors influence the course of the disease. The psychosocial component and association with other diseases pose a challenge for healthcare systems all over the world. Epidemiologic research offers diverse numbers on the prevalence of psoriasis, due to its remittent-relapsing nature and different presentation and severity. Estimates claim that around 2-4% of the population in western countries are affected and Caucasians seem to be rather affected than other ethnic groups. Psoriasis appears to be rare in children before the age of 9 years and have a peak around 20-29 years and another at the age of 60 with a subsequently diminishing incidence. No conclusion has been found on sex preference (17). Epidemiologic studies have identified numerous comorbidities in patients suffering from psoriasis, namely cardiovascular diseases, obesity and dyslipidemia. Furthermore, they have a higher incidence of Crohn disease than control groups (13).

In regards to pathogenesis the acquired, as well as the innate immune system, seem to play a role. The substantial involvement of T cells in the pathogenesis can be observed in different fields. Firstly, activated oligoclonal Th1 cells can be found in tissue samples. Secondly, psoriasis responds in an expected way to drugs, for instance with improvement of symptoms under therapy with cyclosporine and worsening under IFN-γ. Also, the appearance of psoriasis in previously unaffected patients after bone marrow transplantation from a psoriasis-affected donor has been observed. On the genetic level it is confirmed that psoriasis is definitely multi-factorial and that probably the presence of multiple psoriasis alleles encoded on different chromosomes is needed for the development of the disease. For instance, the HLA complex is deduced from over 200 genes. Several HLA antigens are increased in patients with psoriasis and it is presumed that the different variants of psoriasis possibly have different patterns of HLA mutation. Studies performed on identical twins show only a concordance of 60-70%. Another pathogenetic key finding in psoriasis is the epidermal proliferation. A drastically increased proliferation in the basal layer with highly accelerated transition times

can be observed. Whereas it usually takes keratinocytes 28 days to reach the surface, this period is shortened to only 3-4 days and presents as shedding of incompletely keratinized scales. Psoriatic T cells produce various mediators, namely IFN-γ, IL-2, IL-17 and TNF-α, which is a different spectrum of mediators than for instance in atopic dermatitis. Attracted by IL-8, C5a and LTB4, which are prevalent in the psoriatic scale, neutrophil granulocytes migrate into the epidermis and form microabscesses. Eventually, EGF and IL-8 seem to stimulate the keratinocyte turnover.

Many factors have been identified to provoke the outbreak of psoriasis. Exogenous factors are in first line physical, specifically any kind of trauma as in surgery, insect bites or even acupuncture. On the endogenous side, streptococcal pharyngitis has been reported to trigger initial and subsequent eruptions of psoriasis. Also drugs can be potential triggers, namely beta-blockers, lithium, ACE inhibitors, chloroquine and NSAIDs (13). Psoriasis also shows seasonal fluctuation, presumably because of UV radiation. For the traditional assumption that psychic stress promotes psoriatic symptoms no satisfactory evidence has yet been found. Theories imply that the initial development of psoriasis has parallels with the one of contact dermatitis in terms of allergen sensitization. Dendritic cells present the processed antigen to native T lymphocytes, which subsequently proliferate and migrate into the skin. Where exactly genetic disposition interferes in this sequence is unknown. Molecular mimicry may also play a role in this process and similarities have been found between streptococcal M-proteins and cytokeratin 17 (18).

Morphology of psoriasis

Clinical features

Psoriasis has a recognizable classical lesion, presenting as an even, round plaque with demarcated margins usually of brick-red colour with flakes, which can easily be removed as a whole. When the flakes are scraped off, tiny punctate bleedings occur due to injury of the superficial papillary vessels – the so-called Auspitz's sign. Depending on the size of the growing lesion different terminology is used, namely psoriasis punctata, guttata and eventually nummularis.

Large plaques may form bizarre, polycyclic lesions. This variant is then called psoriasis geographica. Psoriasis may even present as erythroderma in extreme cases. Lesions in a linear assembly may be a hint for an artificial or posttraumatic cause. The appearance of such lesions is called Köbner phenomenon. Although only causing slight pruritus, the dryness of the skin may lead to painful rhagades, preferably in proximity to joints. Scratching artefacts, eczema and secondary infections are uncommon. Regression of the lesions can be observed after therapy or spontaneously. Lesions may either regress from the periphery, or from the center, the latter leaving annular residues. After healing, a hypopigmented macule develops, but then vanishes after several weeks.

Psoriasis also has typical predilection sites. The extensor sides of knees and elbows are most commonly affected, as well as the capillitium and sacral region. Variants, as the psoriasis inversa, show different patterns (18).

Despite of the occasionally intense affection of the scalp, neither hair loss nor anomalies of the hair shaft seem to happen. On the other hand, the nails are frequently involved and show recognizable changes. Patients who suffer from psoriatic arthritis are more likely to be severely affected. Psoriasis pustulosa can cause the loss of the nail due to pustules in the nail bed. Oral mucosa is spared, whereas in the course of psoriasis inversa anogenital mucosa may present lesions particularly difficult to treat.

Normally, plaque-psoriasis presents without any systemic involvement with exception of psoriatic arthritis. Nevertheless, arteriosclerosis, hypertension, diabetes and adipositas fit the picture of the average patient suffering from psoriasis. Blood tests tend to be normal, but in patients with a flaring disease, increased acute-phase proteins and blood sedimentation rates, as well as discrete iron deficiency or hypoalbuminemia can be found.

Disease activity is measured to create therapy plans and observe the success of the therapy. The amount of affected body surface and erythema, flaking and induration of lesions is taken into account. Psoriasis can usually be clinically diagnosed and biopsies are evitable in most of the cases. However, single lesions or only subtle manifestation may pose a challenge (18).

Histological features

On a microscopic level, changes analogous to the clinical presentation and transformation of the developing lesion can be found. In early lesions mainly dermal changes take place. Characteristically, the capillaries become dilated and tortuous, especially in the superficial papillary dermis and an edema evolves. Lymphocytes are initially seen in proximity to the vessels and later on migrate into the lower epidermis, which leads to spongiosis. As a result the focal vacuolation leads to disturbance of the epidermal architecture and loss of the stratum granulosum. Eventually parakeratotic mounds are formed. Neutrophil granulocytes continue to migrate into the stratum corneum, finalizing the process. The evolved plaque presents a characteristic picture with marked acanthosis of the elongated epidermal ridges. The papillae are edematous. Both the epidermal ridges and papillae appear to have club-shaped endings, which may merge in established lesion. Throughout the whole epidermal surface parakeratosis can be seen and the suprapapillary plate is thinned. Again, the stratum granulosum becomes not definable. Numerous mitoses can be watched in the suprabasal layers. In palmar and plantar lesions vesiculation and marked spongiosis may be found. Another typical finding is the Munro microabscess in the stratum corneum, formed by irregularities and polymorphisms. The spongiform Kogoj pustules beneath the keratin layer contain neutrophils and some lymphocytes and are not clearly separated from the surrounding epidermal cells (15).

OCT and psoriasis

When viewing psoriatic patches in OCT, parakeratosis depicts as a strong entrance signal, which sometimes has a few parallel layers. This is due to the mixture of poorly and highly differentiated keratinocytes. The mature cells tend to backscatter the light more intensely. Since psoriasis is accompanied by hyperkeratosis, the backscattering is generally stronger in the superficial layers, thus reducing the achievable depth of OCT images. Still, these keratin masses can be well identified and interpreted as a feature. Intraepithelial accumulations with signal intense structures may be interpreted as Munro's micro abscess. Inflammatory cells can be traced in the upper dermis (2). In psoriatic lesions with severe scaling interpretation of the images is not promising.

The dermoepidermal junction appears separated to some extent. Homogenous dark regions can be seen in the dermis, corresponding with dilated blood vessels (19). When trying to determine the epidermal thickness, measuring poses difficult due to psoriasiform papillomatosis. In addition, the dermis appears darker because of the ongoing inflammatory reactions. These circumstances make the definition of a second peak for measuring challenging. Nevertheless, assumptions can be made that OCT will establish as a useful tool for determination of disease activity and response to therapy (2).

Nummular eczema

Epidemiology and pathogenesis

An eczema is a reaction pattern of the skin caused by allergy or contact with toxic substances and may be acute or chronic and has several subtypes, such as the nummular eczema (20). Due to its indistinct definition epidemiologic studies show varying results. Whereas some authors claim it to be rather a disease of the elderly, others feel it is a disease of the middle aged or infants.
The etiology of nummular eczema remains unknown. It is suspected that an allergy to bacterial antigens leads to the development of the disease, similar to allergic contact dermatitis but with circulating antigens from an infection or focus. In patients with a known focus, elimination of the focus did not bring the expected improvement of the nummular eczema symptoms. Secondary infection of the lesions is not uncommon and evidence for the presence of antibodies against staphylococcal antigens was found. The possibility of allergies against bacterial components could be proven in the laboratory but its significance *in vivo* is uncertain. Nummular eczema is more common in patients with atopic dermatitis and severe forms can be observed in patients with hepatitis after treatment with pegylated IFN- α and ribavirin (13).

Morphology of nummular eczema

Clinical features

Clinically, early lesions appear as small erythematous plaques with marked borders and are often rather palpable than visible. In the course scales and vesicles develop, which eventually rupture, leading to yellowish crusts. Occasionally patients complain of severe pruritus. Developed lesions easily reach 5 cm in diameter and present as characteristic nummular plaques. The distribution of the lesions is diverse, ranging from only few lesions to an extensive symmetric flare-up. Typically, lesions are mainly found on the legs and trunk. Regression of the eczema happens to be without scarring and with only mild pigmentary changes and without any systemic involvement. The mucosa is spared (13).

Histological features

Nummular eczema has the pathohistological appearance of spongiotic dermatitis. The pathological changes are found both in the epidermis and dermis and their emphasis often depends on the stage of the lesion and therefore different features appear at different stages. Defining a subtype of eczema by means of histological features may prove difficult and clinical aspects of the disease are more often the key to diagnosis. The most important histological finding is spongiosis. At first, intercellular spaces widen, leading to abnormal intercellular bridges. Then fluids accumulate and finally form an intraepidermal vesicle, accompanied by lymphocytic infiltration of the epidermis. Severe reactions may present with separation of the epidermis from the dermis, resulting in a vesicle. Since the lesions are vulnerable they often become superimposed with bacterial or fungal infections, which lead to a very different picture due to signs of inflammation and pustules. In addition epidermal proliferation reacts with some variety, ranging from acanthosis to psoriasiform epidermal hyperplasia. Parakeratosis and hyperkeratosis may also be present. The dermis is typically edematous and the vessels in the upper dermis are surrounded by a highly variable inflammatory infiltrate. In allergic contact dermatitis, eosinophil granulocytes may be dominant. Throughout the course of the disease, three histologic types can usually be classified. Acute lesions preferably present with blisters and vesiculation.

Additionally, acanthosis can be seen in subacute lesions. Chronic lesions show a rather subtle spongiosis and only rarely vesicles, but marked acanthosis and a psoriasiform pattern (15).

OCT and dermatitis

It has been shown that inflammatory changes can be evidently identified in OCT pictures (2). There are also hints that it is possible to differentiate irritant from allergic contact dermatitis and to measure disease activity (21). Acute spongiotic dermatitis shows a thickened epidermis due to spongiosis, but no hyperkeratosis or acanthosis. The reflectivity of the tissue was decreased, probably due to both intracellular and extracellular edema. Intraepidermal microvesicles can be observed, as well as dilated blood and lymphatic vessels surrounded by an inflammatory infiltrate. Subacute spongiotic dermatitis also shows epidermal thickening. There is no significant hyperkeratosis, but in contrast to the acute form it presents with acanthosis and elongation of the rete ridges. Further, spongiotic vesicles and a perivascular infiltrate can be seen. The chronic form presents with hyperkeratosis and localized parakeratosis. Spongiosis is less marked than in earlier stages. Acanthosis and a thickened papillary dermis can be seen (9).

Study aims

Actinic keratosis, Bowen's disease, superficial basal cell carcinoma, psoriasis vulgaris and nummular eczema may present as erythematosquamous lesions. As their treatment varies significantly, an accurate differentiation between these entities is required. Although clinical examination, possibly coupled with dermoscopy, may increase the clinicians' diagnostic accuracy, the value of OCT in their differential diagnosis has not been formally tested. With reference to current relevant literature (2015) we aimed to define morphological criteria identifiable in Optical Coherence Tomography of the respective diseases and tried to assess the value of Optical Coherence Tomography in the diagnosis of the aforementioned diseases.

MATERIAL AND METHODS

Consecutive indoor or outdoor patients over 18 years attending the Department of Dermatology, Medical University of Graz, with a clinical or histopathologically proven diagnosis of actinic keratosis, Bowen's disease, superficial basal cell carcinoma, psoriasis vulgaris and nummular eczema were included. All participants were informed about the study aim, the procedure of image acquisition and had to give written consent before any study related investigations were performed. Anonymity of patients was guaranteed by assigning each patient to a specific number. Participation in the study did not affect in any way the routine treatment of the patient. Inflamed, ulcerated or painful skin was a reason for exclusion. A medical student under the supervision of a board-certified dermatologist carried out all examinations. The study was conducted during a 15-month period from July 2014 to October 2015.

Process of image acquisition

Each patient received a full body skin examination in order to select the most representative lesion for the subsequent OCT examination. All lesions were macroscopically and dermatoscopically photographed using a digital camera (Canon®) and a mobile dermatoscope (handyscope by Fotofinder ®) with 20-fold magnification, attached to iPhone ®. All pictures were stored in the clinical photography archive of the Department of Dermatology, Medical University of Graz. In case of a wider distribution or multiple lesions a suitable spot was selected and tagged with a reinforcement ring. For the OCT image acquisition, a contact gel (AGFA Skintell Optical Gel ®) was sparingly applied with a pipette (Handystep ® by BRAND). Then image acquisition with the High Resolution Optical Coherence Tomograph (AGFA Skintell ®) was performed according to the instructions in the manual. AGFA Skintell ® acquires images with a lateral and axial resolution of 3 µm. It has a field of view of 1,8 mm x 1,5 mm and a penetration depth of up to 1 mm. Images of poor quality caused by artefacts from air bubbles or very scaly skin were excluded.

Process of image interpretation

All images were subsequently evaluated by a medical student trained in OCT and under the supervision of a board certified dermatologist on a large computer screen. The student was blinded for the clinical and histological diagnosis. The OCT 3D-voxel images were systemically investigated for the presence or absence of the defined OCT features and the results were documented in Excel ®. The histological diagnoses were then retrieved from available medical records in the MEDOCS ® healthcare software.

Definition of the OCT features

Actinic keratosis/Bowen's disease

The applied and analysed OCT features for actinic keratosis were used from available online sources (10), (14), (22). We decided to include the category "Bowen's disease" into the group of actinic keratosis because it presents still an in situ stage in the progression of keratinocyte skin cancer. Moreover, only few reports on the OCT features of Bowen's disease have been published.

Basal cell carcinoma

OCT features and algorithm for basal cell carcinoma were taken from available online sources (11), (23), (24). The algorithm is shown in figure 5.

Psoriasis

OCT features of psoriasis were taken from available online sources (10). Additional features were defined in accordance to histopathological findings of psoriasis.

Nummular eczema

We could not find any research on OCT features of nummular eczema. Because of pathohistological similarities we decided to apply OCT features of spongiotic dermatitis (9).

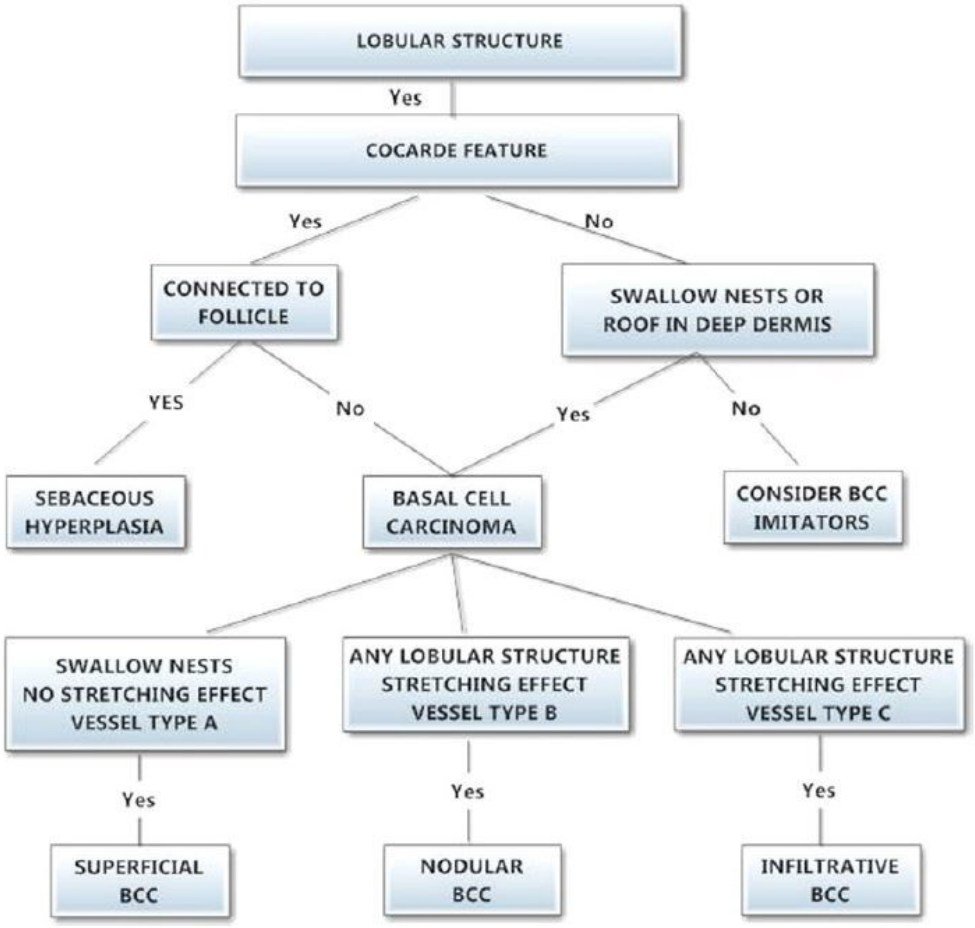


Fig. 5 HD-OCT algorithm for discrimination of basal cell carcinomas from imitators and differentiation between subtypes.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 22 ® and Microsoft Excel 2013 ®. Examined data was depicted in contingency tables and a chi-squared test was applied. Statistical significance was further evaluated with Fisher's exact test. A 2-sided P value of 0,05 was considered to be statistically significant. Sensitivity, specificity, positive predictive value and negative predictive value were calculated with a formula in Excel ®.

RESULTS

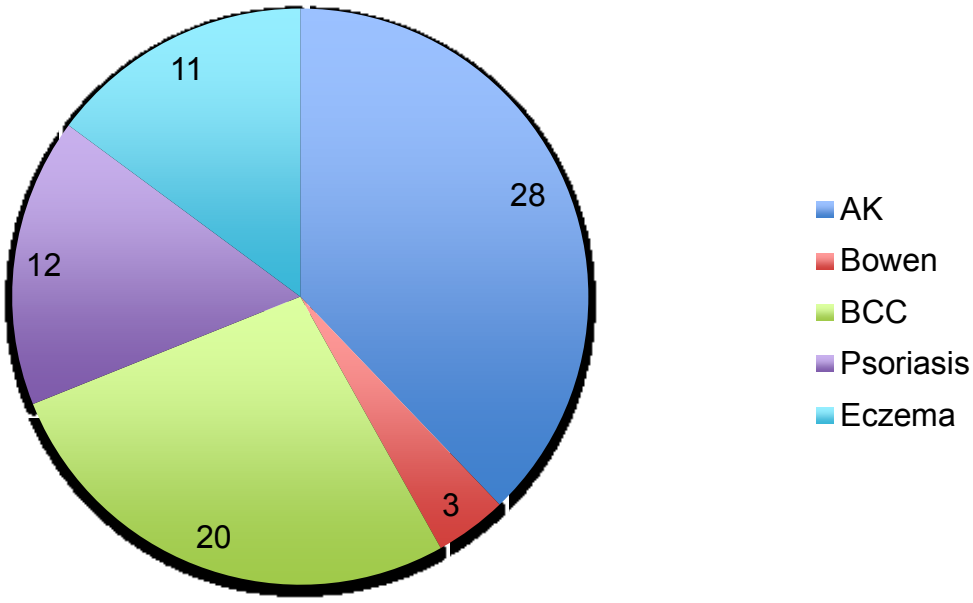
In total, 56 participants were recruited and 96 erythematosquamous skin lesions were imaged by OCT. Of those, 22 lesions were excluded due to an equivocal clinical diagnosis (16 cases) or poor image quality (6 cases). After all, 51 participants presenting with 74 lesions depicted in 220 HD-OCT 3D images were included. The mean age of the study cohort (51% male, 49% female) was 73 years (±15,7 years). Out of the 74 included lesions, a histologically verified diagnosis was found in 54 cases and a distinct clinical diagnosis existed in 20 cases.

The images were examined for the presence of 30 defined OCT features. The most common and established features were statistically analysed to identify morphological findings possibly useful for the differential diagnosis of erythematosquamous skin lesions with OCT. For the basal cell carcinoma group, an algorithm by Boone et al. was applied (11). We also propose an algorithm for OCT for the differential diagnosis of erythematosquamous plaques.

Frequency of the individual diseases

The overall frequencies of diagnoses for the 74 lesions are shown in table 1. Twenty-eight (38%) lesions were actinic keratoses, 20 (27%) basal cell carcinomas, 12 (16%) psoriasis, 11 (15%) eczema and 3 (4%) Bowen's disease.

Table 1 Frequency of the individual skin conditions.



Overall frequency of the evaluated OCT features

The overall frequency of 30 OCT features of the 74 erythematosquamous plaques is shown in table 2. The most common alterations of epidermal architecture were mildly atypical honeycomb pattern, parakeratosis and hyperkeratosis, occurring in over 70% of the cases. There was an outlined epidermal junction in 91% of the cases. With regards to tumour associated structures, lobular structures were identified in 36% of the cases. Inflammatory cells and increased vasculature could be observed in over 30% of the cases.

Table 2 Frequency of HD-OCT features of 74 erythematosquamous plaques.

Feature	AK/Bowen	BCC	Psoriasis	Eczema	Total
Acanthosis	23 (74%)	3 (15%)	12 (100%)	10 (91%)	48 (65%)
Parakeratosis	27 (87%)	11 (55%)	11 (92%)	7 (64%)	56 (76%)
Hyperkeratosis	26 (84%)	10 (50%)	9 (75%)	7 (64%)	52 (70%)
Acantholysis	10 (32%)	5 (25%)	1 (8%)	3 (27%)	19 (26%)
Spongiosis	3 (10%)	3 (15%)	4 (33%)	1 (9%)	11 (15%)
Dark finger-like structures	11 (35%)	5 (25%)	8 (67%)	9 (82%)	33 (45%)
Inflammatory cells	17 (55%)	5 (25%)	2 (17%)	2 (18%)	26 (35%)
Papillomatosis	3 (10%)	2 (10%)	10 (83%)	7 (64%)	22 (30%)
Outlined DEJ	27 (87%)	20 (100%)	12 (100%)	8 (73%)	67 (91%)
Mildly atypical honeycomb pattern	26 (84%)	16 80%)	11 (92%)	7 (64%)	60 (81%)
Severely atypical honeycomb pattern	1 (3%)	-	-	-	1 (1%)
Increased vasuclarization	5 (16%)	11 (55%)	6 (50%)	1 (9%)	23 (31%)
Short fine vessels type A	1 (3%)	2 (10%)	-	-	3 (4%)
Small branched vessels type B	1 (3%)	3 (15%)	-	-	4 (5%)
Large branched vessels type C	3 (10%)	6 (30%)	6 (50%)	1 (9%)	16 (22%)
Lobular structures present	10 (32%)	17 (85%)	-	-	27 (36%)
Lobules with cockade	5 (16%)	13 (65%)	-	-	18 (24%)
Lobules connectd to epidermis	1 (3%)	10 (50%)	-	-	11 (15%)
Lobules not connected to epidermis	8 (26%)	12 (60%)	-	-	20 (27%)
Lobules connected to adnexa	2 (6%)	1 (5%)	-	-	3 (4%)
Small epidermal projections	6 (19%)	7 (35%)	-	-	13 (18%)
Stretching effect	4 (13%)	13 (65%)	-	-	17 (23%)
Perivascular inflammation	3 (10%)	1 (5%)	7 (58%)	2 (18%)	13 (18%)
Hyper- and parakeratosis	24 (77%)	9 (45%)	9 (75%)	6 (55%)	48 (65%)
Atrophy alternating with hypertrophy	11 (35%)	2 (10%)	-	-	13 (18%)
Hypertrophic psoriasiform image	1 (3%)	1 (5%)	9 (75%)	7 (64%)	18 (24%)
Interface lichenoid-like image	-	-	-		-
Typical cockade image absent	2 (6%)	-	-	-	2 (3%)
Budding (cross sectional)	2 (6%)	-	-	-	2 (3%)

Diagnostic value of the OCT features for the diagnosis of erythematosquamous plaques

Results for actinic keratosis and Bowen's disease

Table 3 summarizes the most common OCT findings of the group of actinic keratosis (including three cases of Bowen's disease). As seen in table 3, the two most common features, atypical honeycomb pattern and hyper- and parakeratosis, revealed no significant correlation with AK/Bowen's disease. Atrophy alternating with hypertrophy was present in 31% of the cases and showed a specificity of 95% ($p<0,001$). Inflammatory cells were found in 55% of the cases and revealed a sensitivity of 55% and a specificity of 79% ($p<0,05$).

Table 3 OCT features of the actinic keratosis or Bowen's disease group.

Feature	n=31	P-value	Sensitivity	Specificity
Atypical honeycomb pattern	27 (87%)	>0,05	87%	21%
Hyper- and parakeratosis	24 (75%)	>0,05	77%	40%
Atrophy and hypertrophy	11 (31%)	0,001	35%	95%
Inflammatory cells	17(55%)	0,003	55%	79%
Lobular structures	10 (32%)	>0,05	32%	60%
Lobules with cockade	5 (16%)	>0,05	16%	70%
Lobules connected to epidermis	1 (3%)	0,02	3%	77%
Papillomatosis	3 (10%)	0,002	10%	56%
Increased vascularization	5 (16%)	0,023	16%	58%

Results for basal cell carcinoma

Among the 74 lesions, 20 cases of basal cell carcinoma were included. Based on the algorithm of Boone et al. for OCT, a correct diagnosis was achieved in 17 cases. Nine cases were incorrectly diagnosed as BCC, but were indeed other erythematosquamous disorders (8 actinic keratoses, 1 case of Bowen's disease). In 3 cases we missed to diagnose a BCC. Overall, 45 cases we correctly identified as not being BCC. We were able to determine that the results are statistically significant at the 0,05 level ($p<0,001$). The results of the statistical analysis are shown in table 4. The characteristics of the 20 BCCs are shown in table 5. Lobular structures were present in 85% of the cases with a sensitivity of 85% and a sensitivity of 81%. The cockade feature could be observed in 65% of the cases.

Stretching effect and small epidermal projections revealed a specificity of 93% and 89% (p<0,05). Increased vasculature was present in 55% of the cases with a sensitivity of 55% and a specificity of 78% (<0,05). Alterations of the epidermal and dermal architecture, such as atypical honeycomb pattern, showed no correlation with BCC.

Table 4

Statistical analysis of the algorithm for BCC	
Sensitivity	85%
Specificity	83%
Positive predicitve value	65%
Negative predictive value	94%

Table 5 OCT features of the basal cell carcinoma group.

Feature	n=20	P-value	Sensitivity	Specificity
Lobular structures present	17 (85%)	<0,001	85%	81%
Lobules with cockade	13 (65%)	<0,001	65%	91%
Lobules connected to epidermis	10 (50%)	<0,001	50%	98%
Lobules in dermis	12 (60%)	<0,001	60%	85%
Lobules connected to adnexae	1 (5%)	>0,05	5%	96%
Stretching effect	13 (65%)	<0,001	65%	93%
Small dark projections	7 (35%)	0,034	35%	89%
Atypical honeycomb pattern	16 (80%)	>0,05	80%	19%
Hyper- and parakeratosis	9 (45%)	>0,05	45%	28%
Atrophy and hypertrophy	2 (10%)	>0,05	10%	80%
Increased vasculature	11 (55%)	0,011	55%	78%
Papillomatosis	2 (10%)	0,025	10%	63%
Inflammatory cells	5 (25%)	>0,05	25%	61%

Results for psoriasis

The 12 cases of psoriasis presented with the findings shown in table 6. The most common findings with a significant correlation were papillomatosis and acanthosis. Papillomatosis revealed a significance of 83% and a specificity of 81%, acanthosis a significance of 100% and a specificity of 42%. Perivascular inflammation was found in 58% of the cases with a sensitivity of 58% and a specificity of 90%.

Table 6 OCT features of the psoriasis group.

Feature	n=12	P-value	Sensitivity	Specificity
Papillomatosis	10 (83%)	<0,001	83%	81%
Acanthosis	12 (100%)	0,006	100%	42%
Hyper- and parakeratosis	9 (75%)	>0,05	75%	37%
Atypical honeycomb pattern	11 (92%)	>0,05	92%	21%
Increased vascularization	6 (50%)	>0,05	50%	73%
Perivascular inflammation	7 (58%)	<0,001	58%	90%
Psoriasiform image	9 (75%)	<0,001	75%	85%

Results for eczema

The 11 verified cases of eczema presented with the findings shown in table 7. The only statistically significant feature was papillomatosis, revealing a sensitivity of 64% and a specificity of 76%. Acanthosis was identified in 91% of the cases.

Table 7 OCT features of the eczema group.

Feature	n=11	P-value	Sensitivity	Specificity
Papillomatosis	7 (64%)	0,013	64%	76%
Acanthosis	10 (91%)	>0,05	91%	40%
Hyper-and parakeratosis	6 (55%)	>0,05	55%	33%
Atypical honeycomb pattern	7 (64%)	>0,05	64%	16%
Perivascular inflammation	2 (18%)	>0,05	18%	83%
Acantholysis	3 (27%)	>0,05	27%	75%
Psoriasiform image	7 (64%)	0,003	64%	83%

Algorithm for the differential diagnosis of erythematosquamous plaques

When viewing erythematosquamous lesions in OCT, the presence of papillomatosis has a sensitivity of 83% for psoriasis and 64% for eczema ($p<0,05$) and a specificity of 81% and 76%, respectively. On the other hand, papillomatosis has a sensitivity of 10% and specificity of 63% for BCC and a sensitivity of 10 % and a specificity of 56% for AK /Bowen's disease ($p<0,05$).

The presence of lobules has a sensitivity of 85% and a specificity of 81% ($p<0,05$) for BCC. There is no significant correlation between the presence of lobular structures and AK or Bowen's disease.

Alternating atrophy and hypertrophy was not present in eczema or psoriasis. There was no significant correlation between aforementioned feature and BCC. However, for AK and Bowen's disease, alternating atrophy and hypertrophy significantly correlated ($p<0,001$) and showed a sensitivity of 35% and a specificity of 95%.

The algorithm has three branches, each comprised of three OCT features. Depending on the constellation of presence or absence of these features, one of three groups of skin conditions should be considered.

The proposed algorithm is shown in figure 6 and the statistical performance is shown in table 8.

Fig. 6 Algorithm for differential diagnosis of erythematosquamous plaques. (*) The term “atrophy” abbreviates “atrophy alternating with hypertrophy”. “Pap.” is an abbreviation for “papillomatosis”.

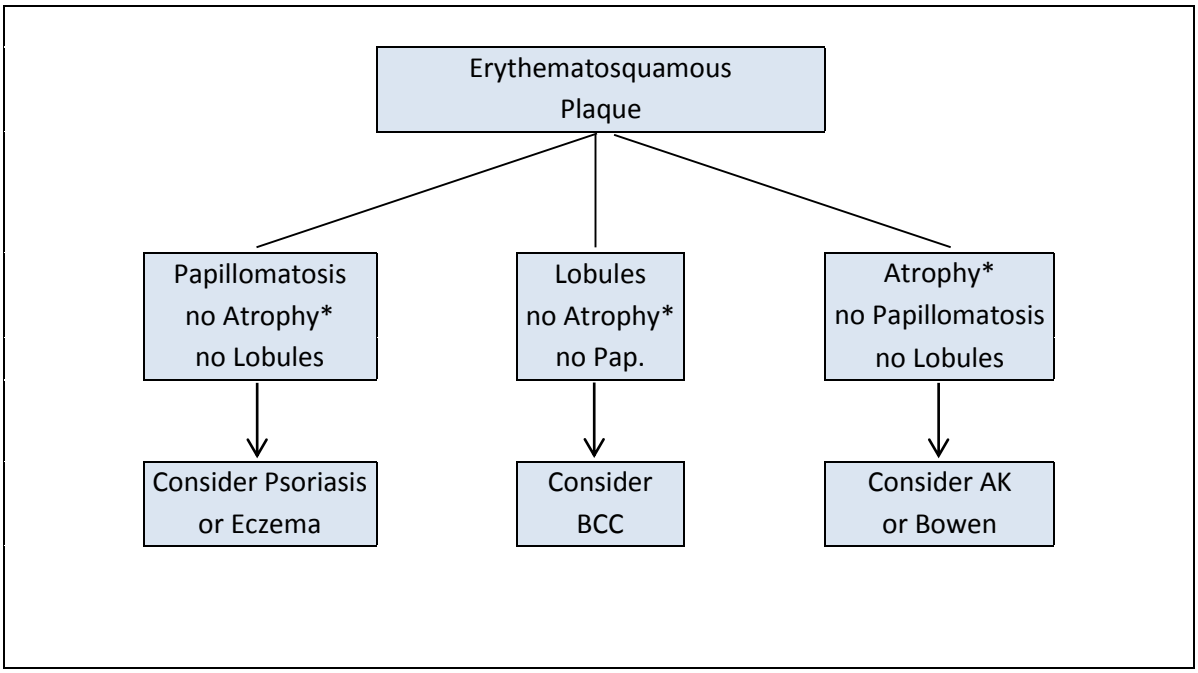


Table 8 Statistical analysis of the algorithm for differential diagnosis of erythematosquamous plaques.

Features	Diseases	P-value	Sensitivity	Specificity
Papillomatosis, no Atrophy, no Lobules	Psoriasis or Eczema	<0,001	83%	85%
Lobules, no Atrophy, no Papillomatosis	BCC	<0,001	65%	83%
Atrophy, no Papillomatosis, no Lobules	AK or Bowen	<0,001	26%	100%

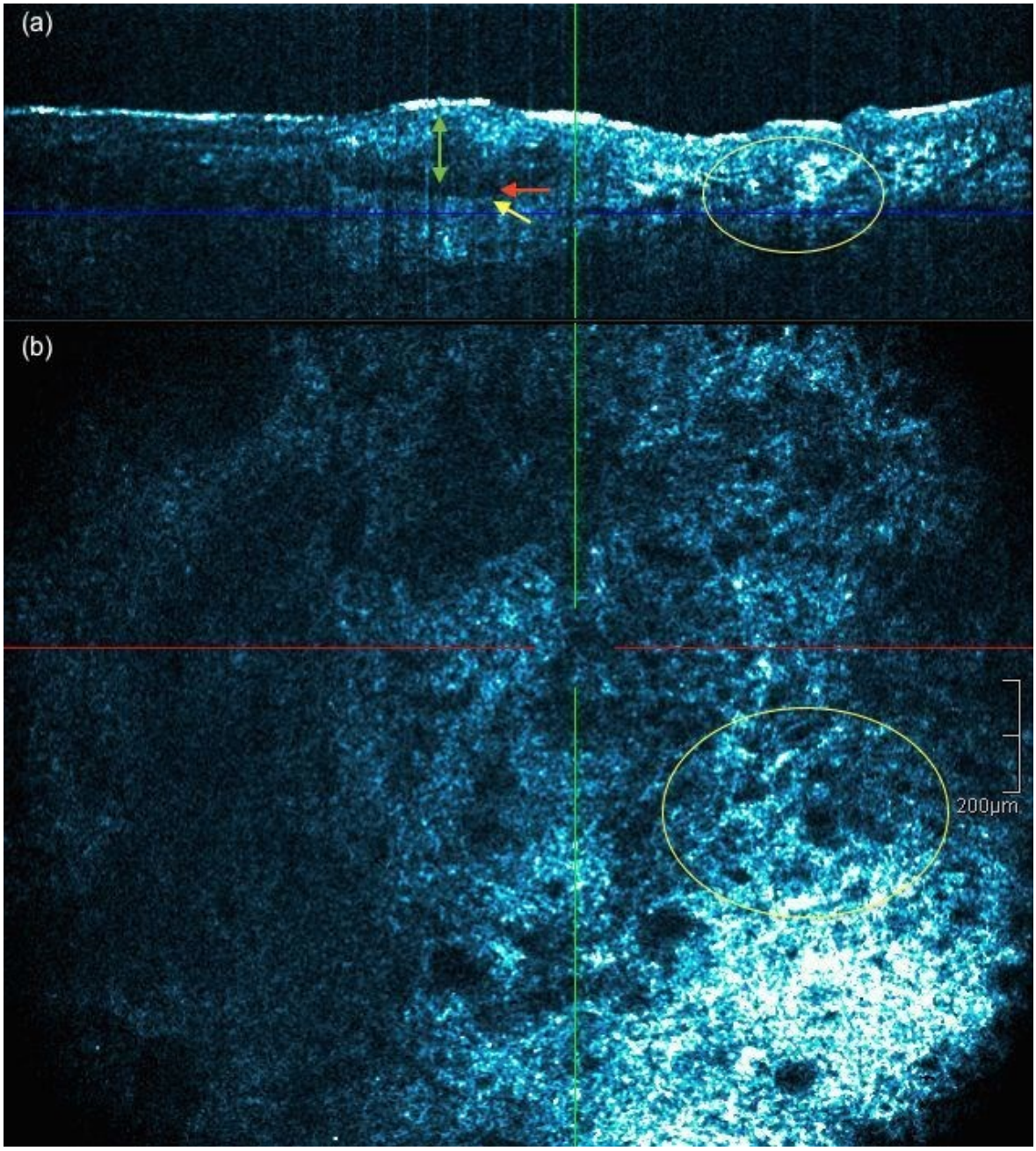


Fig. 7 Tumorous structure. In cross-sectional view (*a*) a lobular structure connected to the epidermis is visible. The typical cockade feature is present, with a peripheral bright ring (*yellow arrow*) next to a dark rim (*red arrow*) surrounding the grey tumor mass (*double- headed green arrow*). Further findings are irregularities in the epidermal and dermal architecture (*yellow circles*) in cross-sectional (*a*) and *en-face* view (*b*).

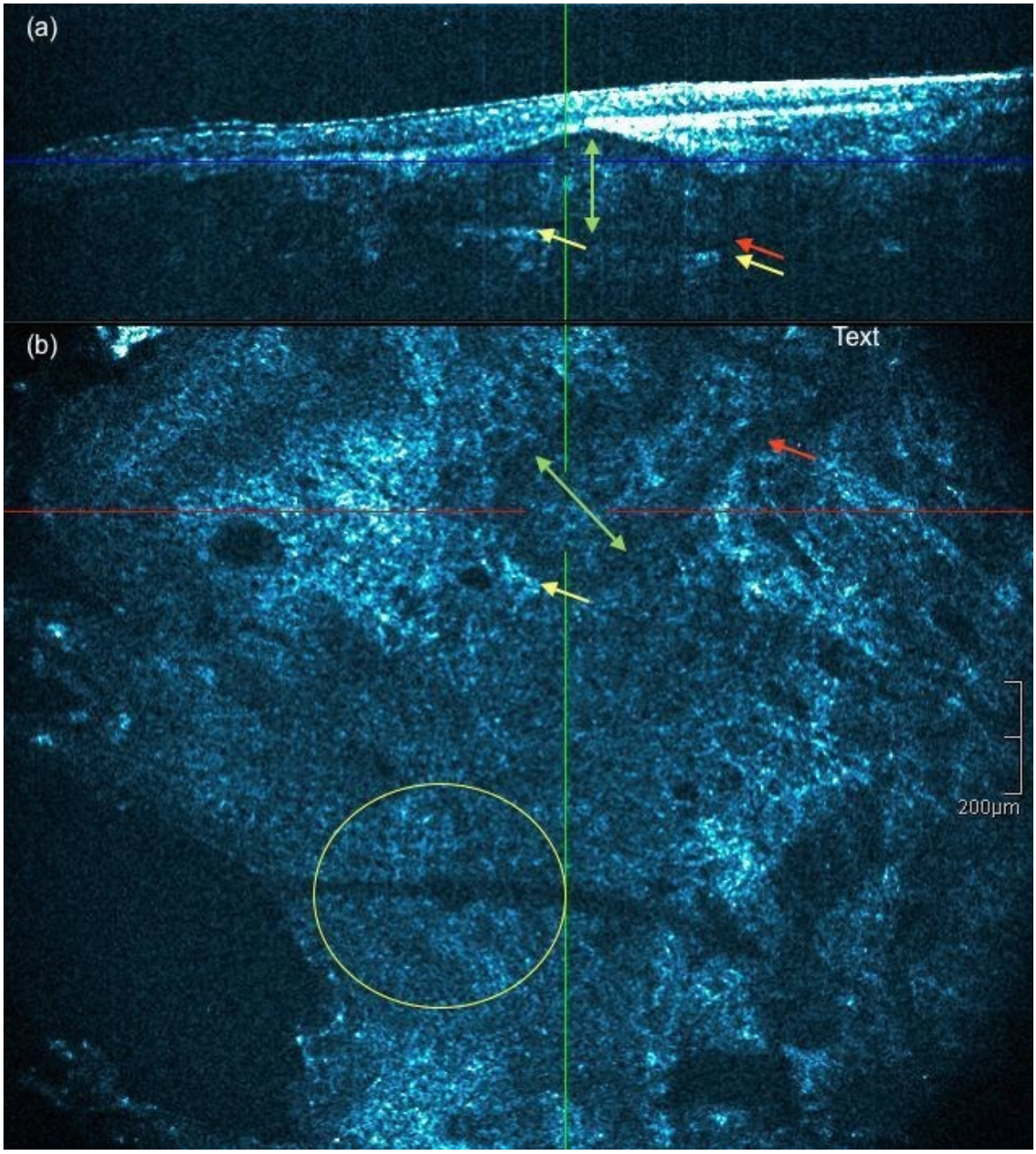


Fig. 8 Tumorous structure. In cross-sectional (*a*) and *en-face* (*b*) view lobular structures connected to the epidermis can be identified. The typical cockade feature is present on both images, with a peripheral bright ring (*yellow arrows*) next to a dark rim (*red arrows*) surrounding the grey tumor mass (*double- headed green arrows*). In addition, the epidermal architecture shows a mildly atypical honeycomb pattern with an artefact produced by a hair shaft lying on the skin surface (*yellow circle*).

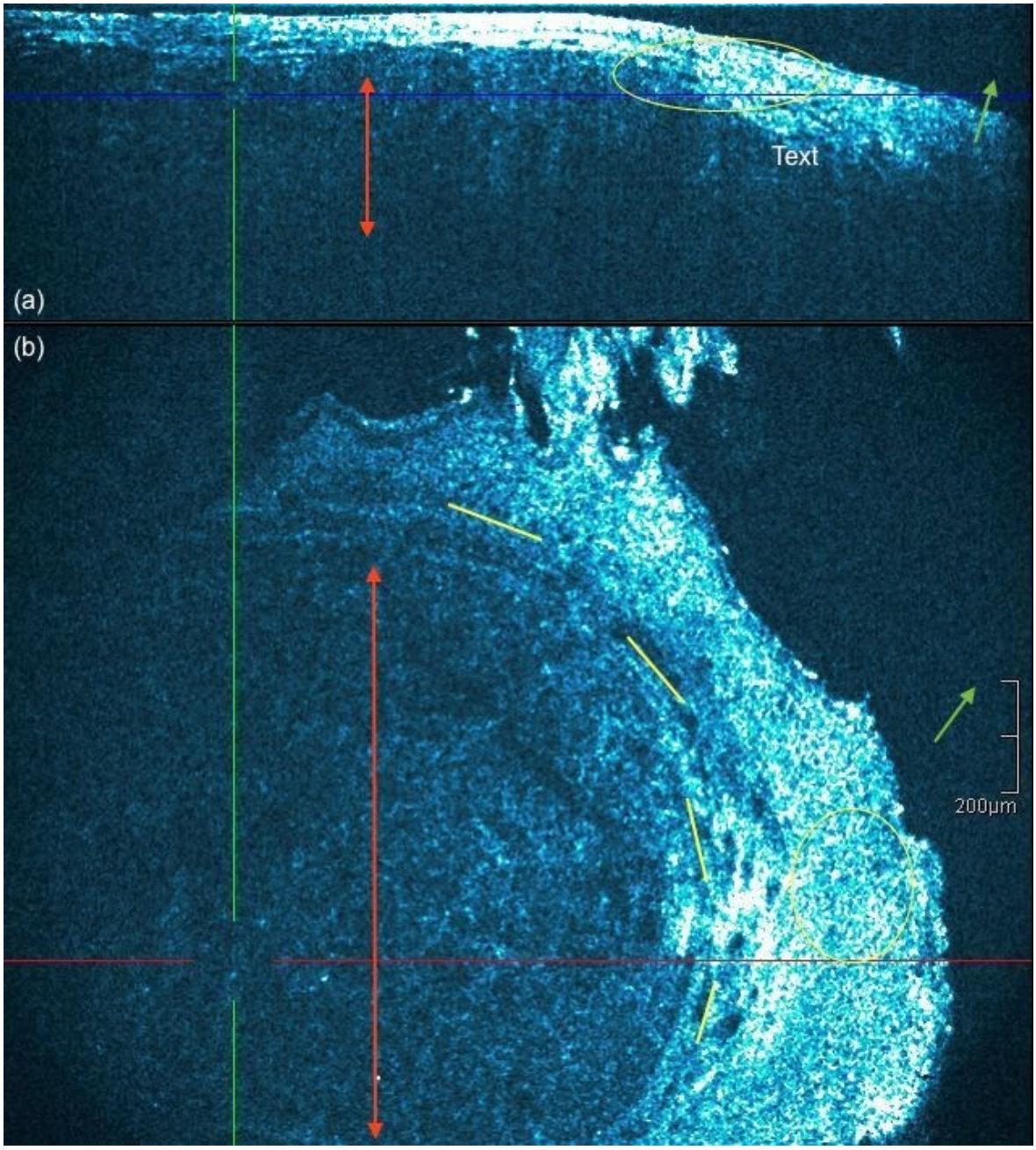


Fig. 9 Tumorous structure. In cross-sectional (*a*) and *en-face* (*b*) view an extensive lobular structure connected to the epidermis can be seen. The tumor mass (*double-headed red arrow*) expands above the skin level making contact gel visible in both images (*green arrows*). It also compresses adjacent structures and lets them appear brighter and thinner than usual (*yellow circles*). Next to the tumor the fibrous stroma is stretched and aligned in parallel bright fibres (*yellow lines*).

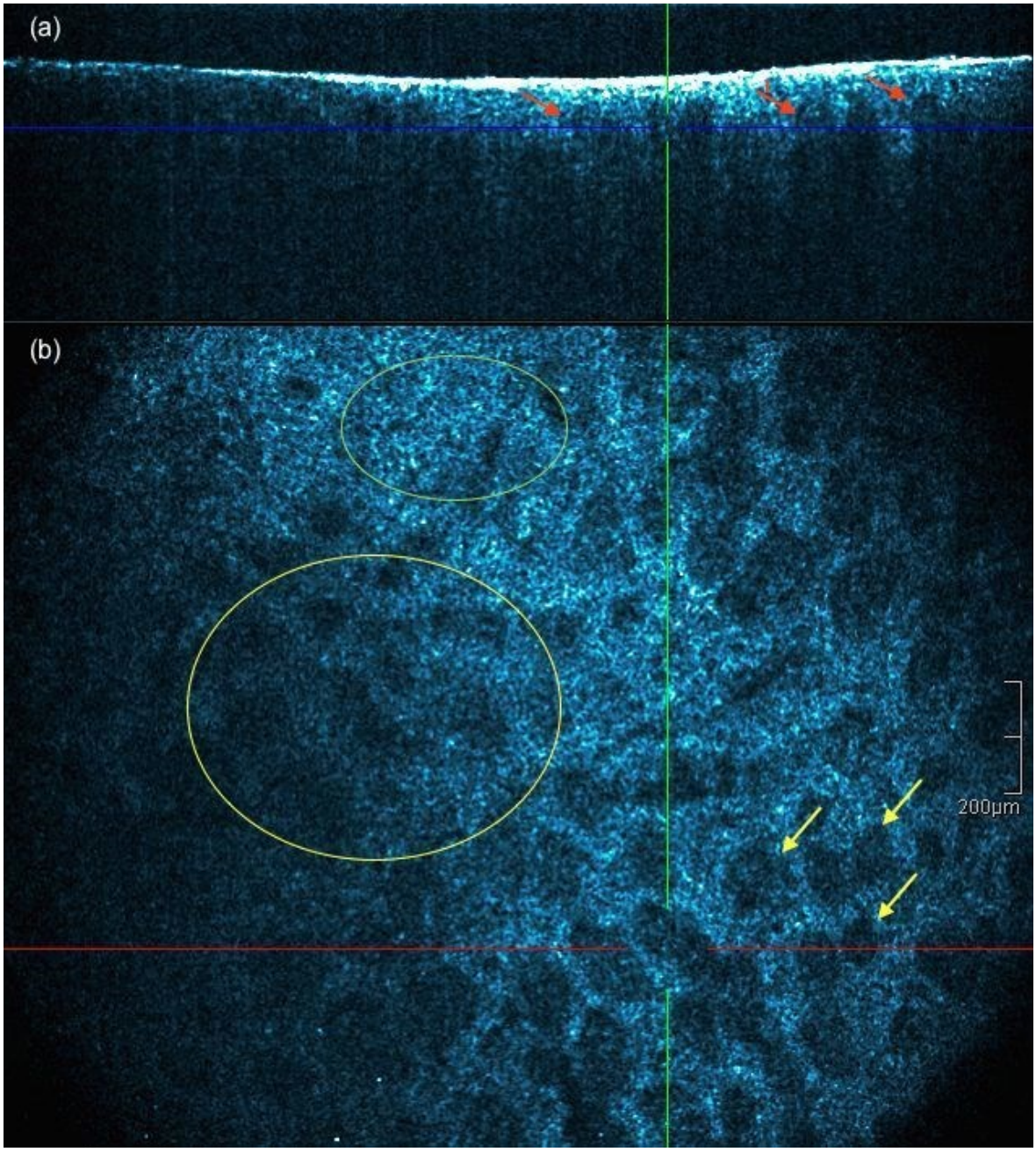


Fig. 10 Psoriasis. Cross-sectional (*a*) and en-face (*b*) view of a psoriatic patch. In cross-sectional view, club-shaped papillae (*red arrows*) and elongated rete ridges are predominant and attenuate other features of the epidermis. Due to acanthosis and papillomatosis the dermoepidermal junction is blurred. In *en-face* view the papillae appear as well-defined, homogenously dark and round structures (*yellow arrows*) and appear to be more densely packed than in normal skin (*yellow circle*). A regular honeycomb pattern can be seen (*green circle*).

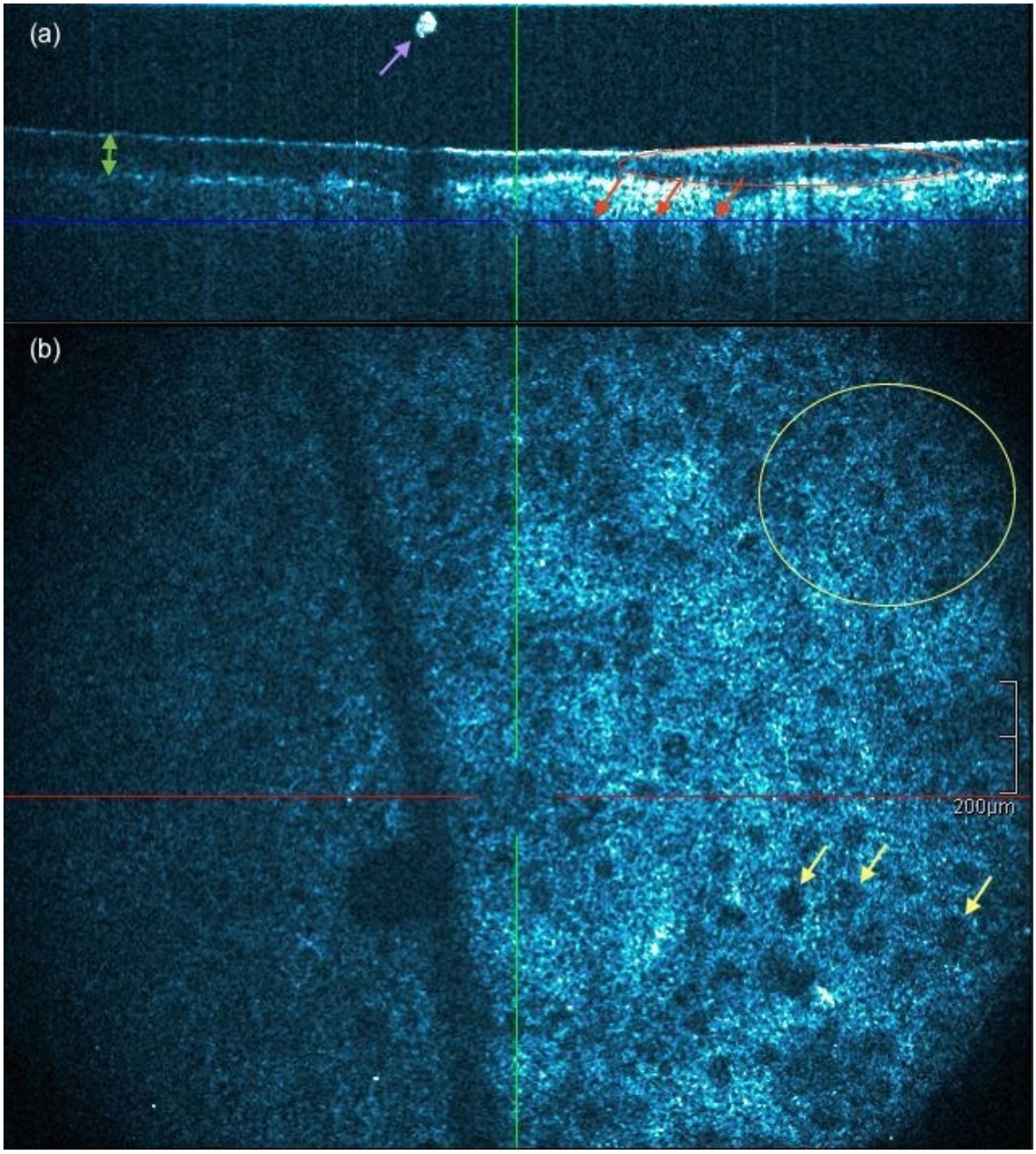


Fig. 11 Psoriasis. Cross-sectional (*a*) and en-face (*b*) view of a psoriatic patch. In cross-sectional view, club-shaped papillae (*red arrows*) and elongated rete ridges are predominant and attenuate other features of the epidermis. Significant Hyperkeratosis presents as a broad dark band beneath the skin surface (*double-headed green arrow*). Parakeratosis depicts as bright spots, corresponding to cell nuclei, in the stratum corneum (*red circle*). Hair shafts (*purple arrow*) and air bubbles produce artefacts, which distinctly worsen image quality. In *en-face* view the papillae appear as well-defined, homogenously dark and round structures (*yellow arrows*) and appear to be more densely packed than in normal skin (*yellow circle*).

DISCUSSION

Erythematosquamous plaques are a very common reason for patients to seek dermatologic consultation. For the dermatologist however, the correct diagnosis and management of these lesions pose a challenge in everyday clinic.
Studies suggest that dermoscopy may aid the diagnosis (25), but the role of OCT has not yet been formally tested in this regard. Eventually, a combination of multiple diagnostic modalities will reduce the need of biopsies, avoid incorrect therapy and accelerate the process of finding a diagnosis.
Up to date, the majority of OCT studies concentrated on the definition of criteria in the realm of non-melanoma skin cancers, which also commonly present as red plaques or patches on the skin (10), (11), (19), (26), (27).
The data obtained by our study extend this current knowledge also to inflammatory lesions such as psoriasis and eczema.
Boone et al. investigated the diagnostic potential of OCT for AK and squamous cell carcinoma in 37 cases and found the presence of hyperkeratosis alternating with parakeratosis in 100% of cases, while atypical honeycomb pattern were present in about 90% of their cases. Other criteria such as atrophy and hypertrophy were present in half of their cases (10). In our study including 31 AKs, we found hyperkeratosis and parakeratosis in 24 (75%) cases, atrophy and hypertrophy was found in 11 (31%) cases, atypical honeycomb pattern was present in 27 (87%). The aforementioned features are suitable to discriminate healthy skin from AK or squamous cell carcinoma (10). Notably, our study highlights that these features are generally very common in erythematosquamous plaques and therefore showed no significant correlation with the diagnosis of AK. For instance, hyperkeratosis and parakeratosis were found in 48 (65%) of our sample of 74 erythematosquamous plaques and in 9/12 (75%) cases of psoriasis.
Another study introduced an algorithm to aid discriminating specific BCC subtypes from clinical imitators. In this sample of 50 BCCs, lobular structures occurred in 48 (96%) cases and lobular structures with the cockade feature in 37 (74%) cases. A stretching effect was observed in 31 (61%) cases and lobular structures connected to epidermis in 16 (32%) and lobular structures *not* connected to the epidermis in 32 (64%) cases (11).

Similarly, we found lobular structures to be present in 17/20 (85%) cases, lobular structures with cockade in 13 (65%) cases, stretching effect in 13 (65%) cases, lobular structures connected to epidermis in 10 (50%) and lobular structures *not* connected to the epidermis in 12 (60%) cases. The defined features for BCC and the algorithm by Boone et al. achieved in our sample a sensitivity of 85% and specificity of 83% and therefore represent useful criteria for the discrimination of BCC from other conditions presenting as erythematosquamous plaques.

Ulrich et al. investigated the sensitivity and specificity of OCT for 235 lesions suspicious of BCC and found a sensitivity of 95,7% and a specificity of 75,3%. Thereby OCT improved the diagnostic accuracy from 65,8% (clinical examination alone) to 87,4% (28). A study by Markowitz et al. with 115 lesions suspicious of BCC, detected a sensitivity of 92,9% and a specificity of 80% for OCT for the diagnosis of BCC (29).

A review reported that the diagnostic accuracy declines when it comes to differentiate BCC from AK (30). This supports the need for an algorithm offering high sensitivity and specificity for the BCC imitators as well.

With regards to psoriasis, OCT poses as a useful tool for monitoring disease activity and treatment response (19) ,(31), (32). However, the characteristic pathohistological appearance of psoriasis might have its analogies in OCT and further research on the morphology of psoriasis in OCT is promising. In our study acanthosis and papillomatosis were very frequent findings, supporting the assumption that these features could represent an important clue for the diagnosis.

In our opinion, OCT will be secondary in the diagnosis of eczema and dermatitis in general, although it may play a role in monitoring treatment response and disease activity (9), (33). Our study included 11 cases of eczema and only papillomatosis correlated significantly with the diagnosis of eczema (sensitivity 64%, specificity 76%). However, the number is too small to draw any definitive conclusions about the diagnostic value of OCT in the diagnosis of eczema.

In summary, a noteworthy amount of established features of certain skin conditions could be clearly observed and correlated with statistical significance. With regards to our proposed algorithm for the differential diagnosis of erythematosquamous skin lesions, further research should be encouraged and the definition of the OCT features needs to be further validated.

Nevertheless, the partition into three groups of skin conditions appears to be practicable. Also, the search for main criteria, as for instance lobules for basal cell carcinoma, may aid the diagnosis.
Overall, OCT appears to be a useful tool for differentiating common skin conditions presenting as erythematosquamous plaques.
However, concerning the implementation of OCT in everyday clinical practice a few issues should be considered.
The recorded area is rather small and practically never captures the whole lesion. Also, the processing of the acquired information interrupts the working flow. Real-time recording with a wider field of vision could improve this matter.
Achieving images of lesions in certain body regions can be challenging due to the construction of the camera. In this case, smaller construction or even combinations with other modalities, as, for instance, dermatoscopy offer a solution. This would also make aiming at an exact spot easier. Different skin regions and skin types might be better visualized with different settings of the OCT, comparable to the diverse ultrasound probes and settings available.
Concerning further research on the use of OCT in the differential diagnosis of erythematosquamous plaques or other skin lesions the following seems suggestive. The appearance and variance of healthy skin in OCT should be thoroughly examined. Particularly features of the elderly skin, which presents with findings such as solar elastosis or atrophy, should be taken into account when defining algorithms. Moreover, the combination with other diagnostic tools, such as dermoscopy or confocal laser scanning microscopy, and creation of algorithms merging the results of the latter could significantly improve the quality of diagnosis.

Limitations

Our study is limited by the relatively small number of cases in each category and by the fact that our algorithm has not been tested in an independent test set of lesions. However, it was the aim of our study to establish specific criteria that aid the differential diagnosis of common entities presenting at times as clinically equivocal skin lesions.

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APPENDIX

Patientenetikett

OCT

Patienteninformation und Einwilligungserklärung zur Durchführung einer Untersuchung mittels Optical Coherence Tomography (OCT, SKINTELL®)

Grundlegendes:

- SKINTELL® ist ein bildgebendes Gerät, mit dem sich beim Menschen Volumen- und Querschnittansichten von der Haut anfertigen lassen.
- Das Licht wird von einer Halogenlampe erzeugt und hat eine Wellenlänge von 1300nm. Es besitzt eine Eindringtiefe von bis zu 1 mm. Das untersuchte Bildfeld ist 1,8 x 1,5 mm groß.
- Die Bilder sind hochauflösend und können Strukturen bis zu einer Größe von 3 µm darstellen.
- Das Verfahren ist nichtinvasiv (ohne Hautverletzung) und ungefährlich.

Vorgang:

- Die zu untersuchende Hautstelle wird markiert (Stift, Klebeetikette,…).
- Auf die Untersuchungssonde wird ein Tropfen Ultraschall-Gel aufgetragen.
- Anschließend wird die Sonde auf die markierte Lokalisation aufgesetzt.
- Nun wird durch den Untersucher die Bildaufnahme gestartet, welche üblicherweise nach wenigen Minuten abgeschlossen ist.

Diagnose/Lokalisation……...

„Ich willige in die Aufnahme mit dem SKINTELL® ein. Außerdem stimme ich einer möglichen Verwendung der Bilder für Lehre, Forschung und allfällige Publikationen - ohne Bekanntgabe meiner persönlichen Daten - zu.“

…….. ……

Unterschrift des/der Patienten/In **Ort, Datum**

…….

Name und Unterschrift Arzt/Ärztin

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der klinischen Studie Verwendung der „Optischen Kohärenztomographie zur …“ teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Einwilligungserklärung

Name des Patienten .....

Geb.Datum: ..... Code: .....

Ich erkläre mich bereit, an der klinischen Studie „ ..... „ teilzunehmen.

Ich bin ausführlich und verständlich über mögliche Belastungen und Risiken, sowie über Bedeutung der klinischen Studie aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung gelesen. Aufgetretene Fragen wurden mir vom Studienarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte des Auftraggebers und der zuständigen Behörden beim Studienarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

.....

(Datum und Unterschrift des Patienten)

.....

(Datum, Name und Unterschrift des verantwortlichen Arztes)