Aus der Klinik für Dermatologie und Venerologie
der Medizinischen Fakultät
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"Eczema in psoriatico": closing the gap between palmoplantar psoriasis and palmoplantar chronic contact dermatitis.

A clinical, histological and immunohistological study.

Dissertation

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Psoriasis and chronic contact dermatitis at the palmoplantar sites cause diagnostic difficulties, especially by isolated involvement. Furthermore, there are many patients with type IV sensitisation, showing contemporarily clinical and histological features of both psoriasis and contact dermatitis (so-called "eczema in psoriatico"). The purpose of the instant study was to compare characteristics of these patients with typical palmoplantar psoriasis and palmoplantar allergic contact dermatitis. The hematoxylin-eosin staining was insufficient for the distinction of these diseases from one another. By immunochemistry, "eczema in psoriatico" presented similar alterations in epidermal hyperproliferation to psoriasis (CK17, Ki67, filaggrin). "Eczema in psoriatico" showed contemporarily overlapping features with psoriasis (IL-8, IL-17 and IL-23) and contact dermatitis (CD1a, MHC I, MHC II, epidermal T cell subsets). Surprisingly, "eczema in psoriatico" revealed a significantly higher number of dermal CD8+ T cells than allergic contact dermatitis and psoriasis. Elevated IgE in serum correlated positively with the number of LCs and negatively with Ki67. Altogether, due to some immunohistochemical constellations, „eczema in psoriatico" (in our opinion a distinct clinical entity of particular importance, with regard to occupational diseases) can be differentiated better from palmoplantar allergic contact dermatitis and palmoplantar psoriasis. Furthermore, our work provides a better understanding of the pathomechanism of psoriasis and allergic contact dermatitis in palmoplantar localisation.

Keywords: psoriasis, contact dermatitis, „eczema in psoriatico", palmoplantar, immunochemistry

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ABBREVATIONS:

ACD: allergic contact dermatitis
APC: antigen presenting cell
CK: cytokeratin
DC: dendritic cell
DP IV: dipeptidyl peptidase IV
E: contact dermatitis
EDTA: ethylenediaminetetraacetic acid
EP: eczema in psoriatico
H&E: hematoxylin-eosin
HLA: human leucocyte antigen
IFN: interferon
IgE: immunoglobulin E
IL: interleukin
KC: keratinocyte
LC: Langerhans cell
MHC: major histocompatibility complex
P: psoriasis
PAS: periodic acid schiff
Tc: T-cytotoxic cell type
Th: T-helper cell type
TLR: toll-like receptor
TNF: tumor necrosis factor

Introduction

Diagnostic difficulties of scaling erythema on palms and /or soles

Psoriasis and chronic eczema at the palmoplantar sites show multiple, overlapping clinical and histological features. Sometimes the differentiation of isolated skin changes on palms and soles, is hardly possible. Histologic parameters vary due to anatomic particularities. Diagnostic difficulties are also combined with heterogeneous aetiology of contact dermatitis, with possible impact of contact allergy, atopy and irritation on clinical picture and therapeutic outcome. Due to mechanical and environmental exposure of hands and feet, psoriatic lesions may change their clinical aspect, and may be influenced by irritation and/or contact sensitisation.

A proper diagnosis is crucial for an efficient therapy and is relevant in case of occupational causal relationship.

Clinical data files from our department distinguish a large group of patients with scaling erythema on their soles and palms that show clinical and histological features of psoriasis and contact dermatitis combined with a high frequency of positive patch tests. This clinical and histological constellation is mostly called "eczema in psoriatico".

Therefore, the purpose of our study was to compare clinical, histological and immunohistological characteristics in patients with typical palmoplantar psoriasis, as well as typical palmoplantar allergic contact dermatitis, and in particular, those showing overlap of both diseases. For a more detailed classification and more aetiological homogeneity, the following patient groups were excluded from this study: cases with chronic irritant non allergic hand and foot manifestation, patients with isolated atopic hand eczema without contact allergy, as well as cases with palmoplantar pustular psoriasis.

Aims of the studies and outline

The objective of this work is a concept validation of eczematous psoriasis (“eczema in psoriatico”) in palmoplantar localisation. This study includes theoretical, clinical and experimental investigations on psoriasis, chronic allergic contact dermatitis and “eczema in psoriatico” in palmoplantar localisation with focus on histology and immunohistochemistry. Results of epicutaneous patch tests will be discussed in detail. The impact of contact allergy on immunohistology is additionally studied.

The theoretical background on epidemiology, clinics, histology and pathomechanism of psoriasis and contact dermatitis is summarised in **Chapter 2**. The focus lies on similarities and differences, when considering anatomical variations of palms and soles. In conclusion to this, the concept of "eczema in psoriatico" is introduced.

Detailed methodology of allergic tests, as well as of histological and immunohistological procedures is provided in **Chapter 3**.

Epidemiological data with focus on clinics and allergy tests is summarised in **Chapter 4**. Major attention is given here to the analysis of frequency of type IV sensitisations with different allergens in all examined groups: psoriasis, allergic contact dermatitis and "eczema in psoriatico".

The subsequent **Chapter 5** presents results of the histological investigations. The frequency of different histological parameters is evaluated quantitatively and compared among all four groups: "eczema in psoriatico", allergic contact dermatitis, psoriasis and healthy skin by investigating palmoplantar skin biopsies (H&E stains).

The most important goal of this thesis is the experimental study by immunohistological methods exploring possible, immunological differences in "eczema in psoriatico" in comparison to allergic contact dermatitis, psoriasis and healthy skin, by investigating palmoplantar skin biopsies with immunochemistry. The results of this study are presented in **Chapter 6**. With the help of different immunostainings, it has successfully been proved, that overlapping immunological processes typical for both psoriasis and contact dermatitis take place contemporarily in "eczema in psoriatico".

The results of this thesis are finally summarised in **Chapter 7**. Clinical implications of the findings, as well as suggestions for further research are discussed in the conclusion.

This thesis gives a new insight into clinical, histological and immunohistological differentiation between palmoplantar psoriasis and palmoplantar chronic contact dermatitis. We distinguish a distinct clinical entity "eczema in psoriatico" with type IV sensitisation and overlapping clinical and histological features of both psoriasis and chronic allergic contact dermatitis. The results allow, to some extent, a better understanding of pathomechanism and differentiation between "eczema in psoriatico", psoriasis and chronic contact dermatitis in palmoplantar localisation. This data is also of importance when an occupational background is given in the patients' disease.

1. Theoretical background

This chapter provides basic aspects of epidemiology, morphology, histology and pathomechanism of psoriasis and contact dermatitis. This chapter also focuses on similarities and differences between both diseases, especially in palmoplantar localisation. In conclusion, an introduction of a new concept of "eczema in psoriatico" will follow.

1.1 Epidemiology

1.1.1 Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease, which is found in circa 2% of the world´s population. Its pathogenesis is not completely understood and includes genetic, environmental and immunological factors. Psoriasis affects men and women equally. The highest incidence rate occurs between the 2nd and 3rd decade of life (type I psoriasis) and in the 6th decade (type II psoriasis) [1]. Nearly 35-90% of patients with psoriasis have a positive family history [2]. A concordance rate in monozygotic twins is significantly higher than in dizygotic twins [3,4]. Psoriasis type I, in contrast to psoriasis type II, often has a genetic background and is associated with various human leukocyte antigens, like HLA-Cw6, HLA-B57, HLA-DR7 [5].

1.1.2 Contact dermatitis

Contact dermatitis is a heterogeneous, multifactorial disease with variable clinical and etiological patterns that affect about 15-20% of the population [6]. Women are affected twice as frequently as men (21.8% versus 12%), which is connected with higher exposure to wet works at the work place or at home [6]. Contact dermatitis has an early onset with its prevalence of 15.2 % in schoolchildren between 12-16 years old [7]. Allergic contact dermatitis causes about 20% of all occupational health complaints [8].

1.2 Morphology

1.2.1 Psoriasis

Clinical manifestation of psoriasis are erythrosquamous scaling plaques found most commonly at the elbows, knees, scalp and groin as well as multiple pitting and dystrophic changes of the nails. The most common clinical variants of psoriasis are psoriasis guttate and

plaque type. One third of psoriatic patients develop psoriatic arthritis.

12% of psoriasis patients are affected on their palms and soles. Isolated palmoplantar psoriasis occurs in 3-4 % of all psoriasis cases [9]. Palmoplantar lesions are usually bilateral, sharply demarcated red plaques with scaling and fissuring and can be palm-sized or distributed as smaller units over palms and soles (Figure 1). Special entities represent palmoplantar pustular psoriasis with erythrosquamous plaques and recurrent sterile pustules.

Nail changes occurs in 25-50% of all psoriasis patients and allows in some cases differentiating psoriasis in hand- and foot localisation from isolated palmoplantar chronic contact dermatitis. Oil spots and onycholysis are specific for psoriasis but rarely occur in eczema. Nail pitting can occur in both psoriasis and contact dermatitis.

The Koebner phenomenon describes the appearance of psoriatic lesions at sites of skin trauma. It is believed that palmoplantar psoriasis is continually influenced by Koebnerisation due to mechanical trauma.

Psoriasis phenomena reflect histological changes. Upon removal of silvery scales, (equivalent to parakeratosis) the surface appears similar to wax flakes (candle phenomenon- "signe de la tache de bougie"). Removal of the latter leads to papillary bleeding (Auspitz´ sign) and corresponds to dilated vessels in the papillary dermis and thinning of the suprapapillary plates [10].

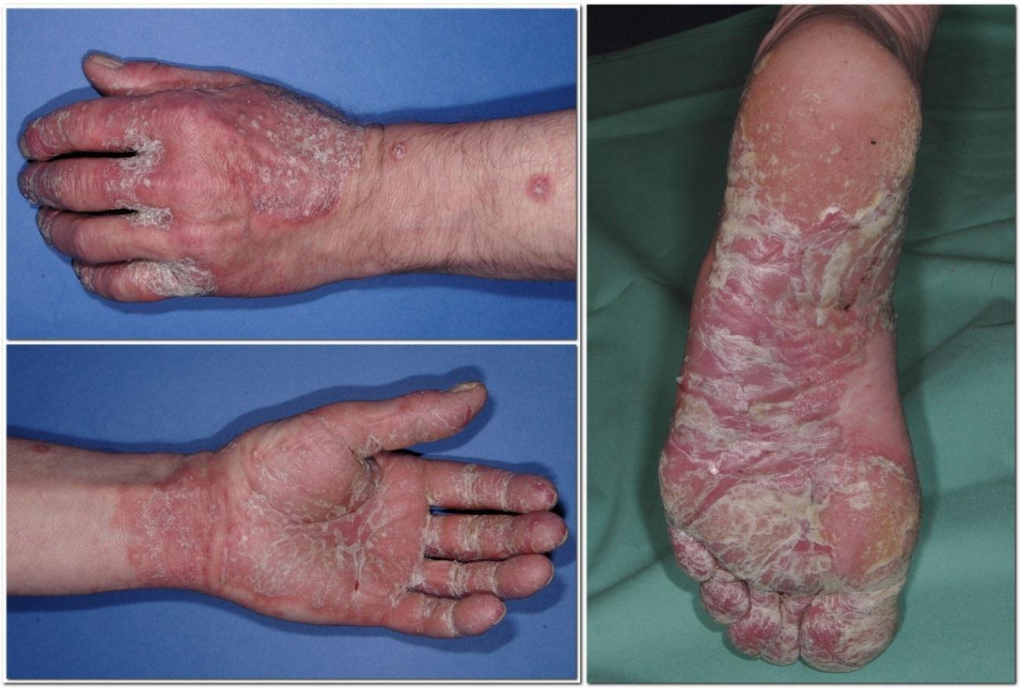

Figure 1. Palmoplantar psoriasis with sharply demarcated erythematous plaques with scaling and fissuring.

1.2.2 Contact dermatitis

Contact dermatitis is characterised through pruritic papular- and vesicular- eruptions on

erythematous ground in acute stadium (Figure 2) and lichenification, erythema, scaling, fissures and excoriations in chronic forms.

Contact dermatitis is often localised palmoplantar. The one-year prevalence of hand eczema in the general population accounts for 14% [11]. Foot dermatitis is estimated for 10% of all cases with contact dermatitis [12] and has an increased risk for developing of polysensitisation [13].

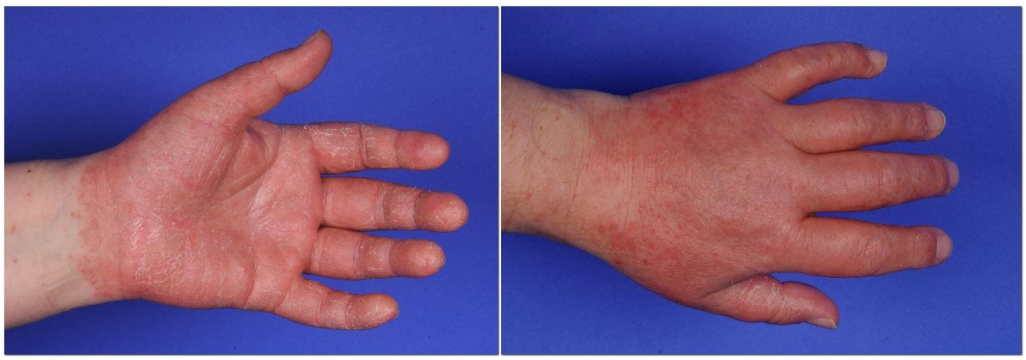

Figure 2. Subacute hand eczema with not sharply demarcated erythema and papulo-vesicular eruptions.

Due to morphology, hand and foot eczema can be divided into vesicular/pompholyx, chronic-lichenoid, hyperkeratotic-raghadiform and fingertip dermatitis. Especially chronic hyperkeratotic-raghadiform form can be clinically and histologically indistinguishable from palmoplantar psoriasis (Figure 3).

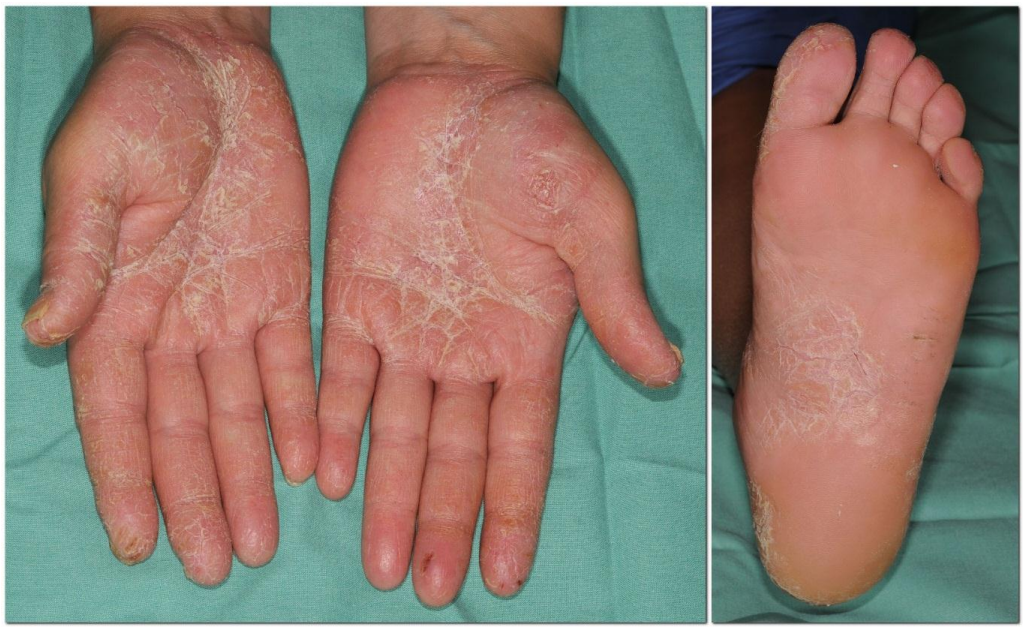

Figure 3. Chronic hyperkeratotic-raghadiform palmoplantar eczema.

Etiology of hand- and foot eczema can result from irritant- or allergic contact dermatitis, from atopic dermatitis or be multifactorial. The clinical picture may not correspond to etiology.

Contact sensitisation is found in less than 1/3 of all cases of hand eczema and may be the

primary cause or complication to irritant or atopic hand eczema. Nickel, cobalt, fragrance-mix, balsam of Peru and colophony are found to be the most common allergens in hand eczema [14].

Concerning feet dermatitis, chromium compounds and adhesives are the most common cause of contact allergy [12].

1.3 Histology

1.3.1 Healthy skin

The skin can be divided into the epidermis- an outer layer and the dermis – an inner layer, which is attached and woven to the subcutaneous fat. The epidermis consists of different cell types of which epithelial cells (keratinocytes) are the most prominent in term of structural features. They can be divided into four layers: stratum basale, stratum spinosum (prickle cell layer), stratum granulosum and stratum corneum. Basal cells are undifferentiated cuboid cells with large nucleolus and basophilic cytoplasm. Prickle cells are polygonal with eosinophilic cytoplasm and oval nuclei. Granular cell layer is characterised by keratohyalin granules. The cells of stratum corneum do not include the nuclei and are flattened. The epidermis renews itself continuously- the transit time of keratinocytes through the epidermis is estimated at 56 days [15].

Dermis consists of collagen and elastic fibres as well as ground substance, and can be divided into papillary (upper) and reticular (lower) layers. Dermis contains fibroblasts, neurovascular network and epidermal appendages, such as hair follicles, sebaceous- and sweat glands [16].

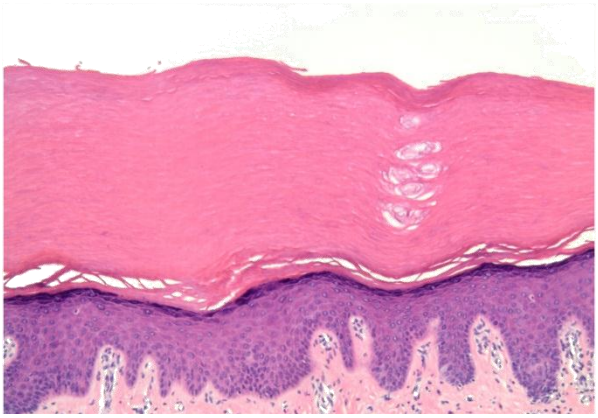

Figure 4. Histology of the palmoplantar skin.

The blood supply in the skin follows throughout superficial- and deep vascular plexus, located respectively in upper- and lower reticular dermis. In contrast to richly vascularised papillary dermis, there are no capillaries in the epidermis and nutrition follows by diffusion [17].

Studies from the last three decades have shown that normal skin contains resident populations of dendritic cells, [18] as well as abundant amounts of T-lymphocytes, which can initiate and maintain immune reactions without additional recruitment of T-cells from the blood [19].

Skin from the soles and palms is characterised by a thickened stratum corneum and prominent epidermal ridge pattern (Figure 4). There are no sebaceous glands and no hair follicles found in the palmoplantar localisation.

1.3.2 Psoriasis

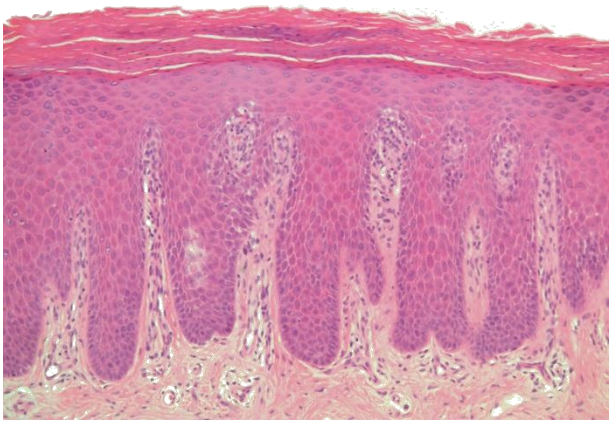

Figure 5. Histology of the palmoplantar psoriasis.

Classical psoriatic plaque lesions show regular acanthosis with elongated and club-shaped epidermal ridges. The suprapapillary plates are thinned. There is a loss or thinning of granular layer, in which terminal differentiation begins. Consequently, incomplete, differentiated keratinocytes retaining a cell nucleus form a stratum corneum, which is known as confluent parakeratosis. The papillary dermis is oedematous and includes tortuous and dilated capillaries. The latter cause visible redness of psoriatic efflorescence. The subpapillary dermis may include a perivascular mononuclear infiltration, including T lymphocytes and dendritic cells. The diagnostic features of psoriasis lesions are "Munro microabscesses" – accumulated neutrophils within the parakeratotic stratum corneum. Another characteristic feature are "spongiform pustules of Kogoj", located beneath the stratum corneum and which consist of accumulated neutrophils [20]. The epidermal cell cycle is shortened in psoriatic skin to 7 days [21]. There is increased number of proliferating cells in the basal cell layer.

Palmoplantar psoriatic lesions may cause diagnostic difficulties because of marked spongiosis. Stratum granulosum is usually normal or thickened in contrary to other localisations. The typical psoriatic pattern is often lacking [22].

Histology of the palmoplantar psoriasis is represented in Figure 5.

1.3.3 Contact dermatitis

Contact dermatitis varies through all its stages including both dermal and epidermal changes. The main characteristic feature is the presence of intercellular oedema or spongiosis, which can lead to the formation of an intraepidermal vesicle or bulla. Another characteristic feature is exocytosis- lymphocytic infiltration of the epidermis. The epidermis is irregularly acanthotic with V-shaped rete ridges. There are multiple foci of parakeratosis and plasma in the parakeratosis. In contrast with psoriasis, stratum granulosum is preserved and there is no thinning of the suprapapillary plates and no oedema of the papillary dermis. In the papillary dermis, there is superficial perivascular lymphocytic infiltration, in some cases with numerous eosinophils. Vessels in the papillary dermis are often horizontal [23].

Spongiotic dermatitis can be divided into acute (with vesiculation and bullae), subacute (with marked acanthosis, spongiosis, vesiculation) and chronic (subtle spongiosis and psoriasiform acanthosis) [23]. Because a thickened stratum corneum at palmoplantar sites blisters can be firm creating pompholyx.

Histology of palmoplantar contact dermatitis is presented in Figure 6.

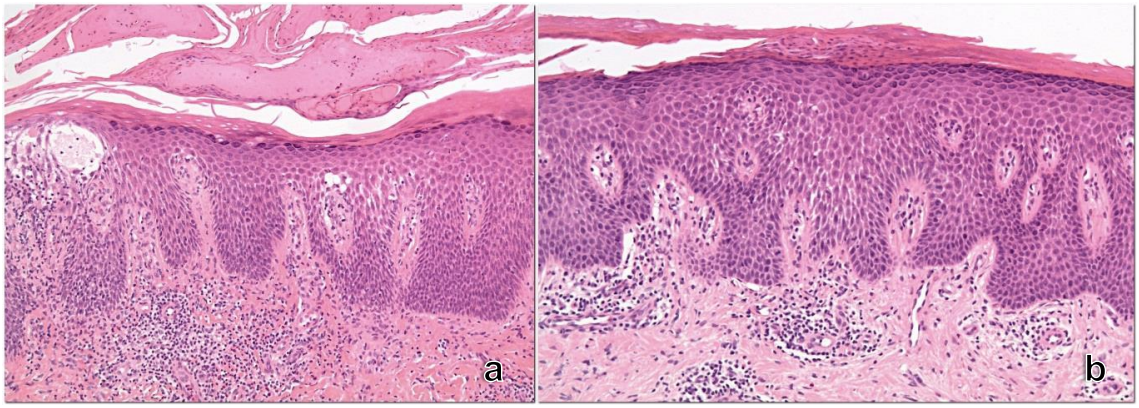

Figure 6. Histology of the palmoplantar contact dermatitis: acute- (a) and subacute phase (b).

1.4 Pathomechanism

1.4.1 Psoriasis

The exact etiology of psoriasis is still not completely understood. Psoriasis belongs to immune-mediated inflammatory diseases and has similarities in pathophysiology with rheumatoid arthritis, Crohn's disease, multiple sclerosis or juvenile-onset diabetes [24]. Psoriatic patients are known to have a higher prevalence of the metabolic syndrome [25] and an increased risk of cardiovascular events [26], which correlate with the severity of psoriasis.

Psoriasis is believed to be result of complex interactions between T lymphocytes, keratinocytes and dendritic cells [24].

T cells play a crucial role in psoriasis and are polarised as Th1, Tc1 and Th17 cells. They release inflammatory cytokines (in case of Th1: INF-γ and TNF-α and in case of Th17: IL-17), which promote further recruitment of immune cells, keratinocyte proliferation, dermal angiogenesis and inflammation [24]. An innate immune system (including cytokines, chemokines, antigen-presenting cells such as neutrophils and Langerhans' cells) also plays an important role in psoriasis by initiating and directing the acquired immune response and supporting the epidermal hyperproliferation [27]. Chemokines produced by keratinocytes (including IL-1, IL-23, Il-17, INF-γ) have an impact on both innate- and acquired immune systems and lead to activation of dendritic cells, neutrophils as well as T cells. Keratinocytes express also MHC-II and may act as non-professional APC [24,27].

1.4.2 Contact dermatitis

Contact dermatitis results from the skin contact to the irritants (irritant contact dermatitis) or allergens (allergic contact dermatitis); in both cases by eventually coexisting atopy. These types of contact dermatitis are, in most cases, clinically and histological indistinguishable [28].

The etiology of hand eczema is as followed: irritant contact dermatitis (35%), followed by

atopic (22%) and allergic hand eczema (19%) [29].

Pathomechanism of irritant contact dermatitis is an unspecific inflammatory reaction due to repeated chemical or physical irritation, which occurs only in the exposed skin [30].

In case of allergic contact dermatitis there are "allergen specific lymphocytes" that initiate the inflammation reaction. Through repeated contact with the allergens, the clinic aggravates and can spread out into the non-exposed skin [30].

Allergic contact dermatitis consists of an induction phase (known also as "afferent" or "sensitising" phase) taking at least 4 days (but generally weeks to months) and effector ("efferent") phase taking from 1 to 4 days.

In the induction phase, allergens (haptens) bind to antigen-presenting cells (epidermal Langerhans cells). Activated Langerhans cells travel to regional lymph nodes, where they are recognised by specific T cells.

Hapten presentation by Langerhans cells depends on the chemical nature of contact allergens. Lipophilic haptens penetrate directly into Langerhans cells. They are processed in an "endogenous way", favoring MHC class I molecules and are recognised by allergen-specific CD8+ T cells. Hydrophilic haptens (for example nickel ions) are processed in "exogenous way" favoring MHC class II molecules and activation of allergen-specific CD4+ T cells [31].

Specific T-cells proliferate in lymph nodes and are released through efferent lymphatic vessels into the circulation.

The effector phase is caused by renewed contact to allergens and leads to clinical manifestation of allergic contact dermatitis. Allergen-specific effector T cells produce pro-inflammatory cytokines, causing arrival of more inflammatory cells and promoting the killing of the haptenised cells [32]. Patch testing is a diagnostic procedure confirming allergic contact dermatitis, in which positive results correspond to an "efferent" phase of allergic contact dermatitis.

1.5 Concept of "eczema in psoriatico"

The concept of eczematous psoriasis has already been discussed by many authors.

In 1991, Epstein et al. distinguished the primary and secondary eczematous psoriasis. The first was believed to be an endogenous process typical for regions such as the groin and axilla. The secondary eczematous psoriasis evolved as a result of exogenous factors such as irritants and allergens. According to this author, the diagnosis of eczematous psoriasis depends on the presence of stigmata of psoriasis [33].

Psoriasis in palmoplantar localisation may be influenced by different environmental factors. It is known, that allergic contact dermatitis can act as Koebner phenomena, maintaining or triggering palmoplantar psoriasis. This is why patch testing is often suggested as a standard examination in that localisation. Lack of responsiveness to psoriatic therapy can also be a manifestation of coexisting allergic contact dermatitis [34].

Patients with palmoplantar psoriasis can develop due to household/environmental and/or occupational exposure contact dermatitis, although this is particularly rare. Consequently, such patients often present overlapping clinical and histological features of psoriasis and allergic contact dermatitis.

The concept of “eczema in psoriatico” is illustrated in Figure 7 and 8.

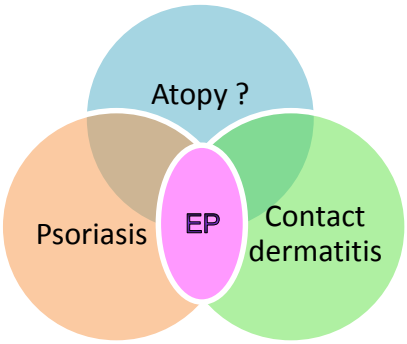

Figure 7. Relation between psoriasis, contact dermatitis, atopy and "eczema in psoriatico"(ep).

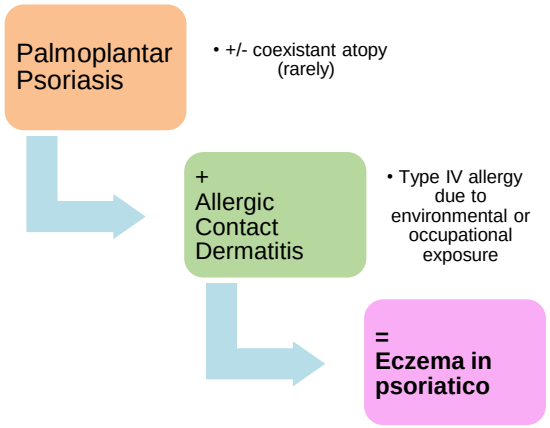

Figure 8. Mechanism of development of "eczema in psoriatico".

1.6 Summary

The purpose of this chapter was to provide basic information regarding psoriasis and chronic contact dermatitis with focus on the particularities of the palmoplantar localisation. Epidemiology, morphology, histology and pathomechanism are described in subsections of this chapter. In order to facilitate the understanding of changes occurring in inflammatory diseases, detailed histology of palmoplantar healthy skin is enclosed. A new concept of “eczema in psoriatico” and its development mechanism are discussed in conclusion.

2. Materials and methods

This chapter provides characterisation of patients as well as detailed descriptions of allergy tests, histologic and immunohistologic procedures. In conclusion, the explanation of statistical methods follows.

2.1 Patients

Two experienced dermatopathologists performed a blind evaluation of 142 palmoplantar skin samples from patients treated in our department between 2000-2012 with a diagnosis of psoriasis, "eczema" or "eczema in psoriatico". Clinical data, allergy tests were retrospectively examined. Cases with chronic irritant non allergic hand and foot manifestation were excluded from this study and investigated separately. Patients with isolated atopic hand eczema without contact allergy, as well as patients with palmoplantar pustular psoriasis, were not included in our study.

59 patients and 63 skin samples were finally selected, in which both examiners had come to the same evaluation of the histopathological diagnoses: 30 patients and 33 skin samples with „eczema in psoriatico", 13 patients with contact dermatitis, and 12 patients with psoriasis . In addition, five samples of healthy skin from 4 patients were selected as a control. Patients with marked positive epicutaneous patch tests results were accordingly classified.

The presence of other classical skin lesions in typical distribution facilitates the diagnosis of psoriasis and contact dermatitis. By most of the cases (23/30 of "eczema in psoriatico", 10/13 of eczema), an isolated involvement of the palmoplantar skin existed.

Tinea manum and pedum were excluded with additional mycological tests, as well as by negative PAS-staining.

2.2 Allergy Tests

All patients (except for control group and four psoriasis patients) were already investigated with the patch test according to routine clinical examination. Patch tests were performed to evaluate the skin sensitivity to standard allergens, such as potassium dichromate, thiuram mix, cobalt chloride, balsam of Peru, wool alcohols, nickel sulfate, PTBP resin, formaldehyde, fragrance mix, paraben mix, methyldibromo glutaronitrile, propolis, mercaptobenzohiazole, fragrance mix II (according to DKG standards; producer Almirall Hermal). In some patients, another patch test screening series like: Cosmetics; Vehicles, Emulsifiers; Preservatives; Disinfectants; Epoxy and Glues; Textile and Leather Dyes; Rubber Chemicals; Corticosteroids; Fragrance; Plants; Dental materials; Hairdressing; Cutting oil I (current);

Metal compounds were performed (data non presented). Patch tests were interpreted according to International Contact Dermatitis Research Group [35] and were applied on the upper back and removed after 48 hours. Readings were carried out on day 2 (48 hours), on day 3 (72 hours), after 96 hours and additionally in doubtful cases on day 6 (144 hours).
Additional allergy tests such as prick-tests and evaluation of total immunoglobulin E (IgE) were performed in some of the patients. Measurement of IgE in serum was based on fluorescence-enzyme immunoassay and investigated by UniCAP 250 EliA (Phadia). The scores were divided as followed: normal range under 100 kU/L, slight elevated between 100 and 500 kU/L, moderate elevated between 500 and 1000 kU/L and strong elevated with more than 1000 kU/L.

2.3 Preparation of tissue samples

Biopsies were obtained from patients seen at the Department of Dermatology and Venereology, Otto-von-Guericke University in Magdeburg by routine dermato-pathological examination and after informed consent. Biopsies taken from the lesions were fixed in 4% neutral buffered formaldehyde (Otto Fischar) and embedded in paraffin. All biopsies were cut and stained with hematoxylin-eosin (H&E) and periodic acid schiff (PAS).

2.4 Analysis of the histological parameters in the stained sections with the hematoxylin-eosin technique

According to our experience and to literature, we chose histological parameters that were considered helpful in the diagnosis of psoriasis and contact dermatitis. Evaluation of H&E-stained sections were done blinded without knowing clinical parameters or clinical diagnosis. Parakeratosis is graded as followed: mild, moderate and strong, occupying accordingly up to 33%, between 33 and 66% and more than 66% of whole stratum corneum. We evaluated the “distribution” of parakeratosis (multiple foci, confluent, para- and orthokeratosis vertically distributed) and its content (only neutrophils, only plasma, or both neutrophils and plasma contemporary). Acanthosis and suprapapillary plates were measured with 10 mm scale under 10x fold amplification. Acanthosis was graded as followed: mild (less than 3.33 mm), moderate (between 3.33 and 6.66 mm) and strong (with more than 6.66 mm). Thinning of the suprapapillary plates was considered when the ratio of thin rete ridges to the total rete ridges was equal or less than one-fifth. We evaluated loss or thinning of granular layer, lymphocytic exocytosis in epidermis, oedema of the papillary dermis and presence of "Munro microabscesses" and eosinophils in the infiltrate. The samples were divided according to the shape of rete ridges (club-shaped, V-shaped or mixed) and capillaries in upper dermis (tortuous, dilated, horizontal or mixed). We measured the grade of spongiosis (lower part of epidermis, full-thickness, spongiotic vesicles) and the grade of infiltrate in upper dermis (mild, moderate or strong).

2.5 Immunochemistry

The following primary antibodies were used: CK16 (clone: LL025; Abcam), CK17 (clone: E3; Dako), CD26 (polyclonal; Abcam), Filaggrin (clone: FLG01; Gene Tex Inc), TLR4 (clone: 76B357.1; Abcam), MHC I (clone: EP1395Y; Abcam), MHC II (monoclonal; Abcam), CD1a (clone JPM30; Leica Biosystems), Ki67 (clone: MIB-1; Dako), CD4 (clone: 4B12; Bi-oGenex), CD8 (clone:C8_144B; Dako), IL-8 (clone: 6217; R&D Systems), IL-17 (polyclonal; Abcam), IL-23 (polyclonal; Abcam), IL-31 (polyclonal; Abcam).

Paraffine-embedded tissue sections were deparaffinised and rehydrated.

The background staining was minimised through the following blocking methods: 10% FCS in DPBS (GIBCO, 14190-094) in case of CD26 and TLR 4; Protein Blocking Pro Taqs (BIOCYC, 400104695) in case of MHC I, MHC II and IL-31 or combination of 0, 25% Tween in 10% FCS in PBS (Roth, 9127.1) and 10% FCS in PBS in case of IL-17.

For antigen recovery in the case of CK16, Filaggrin, TLR4, IL-17, IL-23, IL-31, citrate buffer pH 6 (Zytomed, ZUC 028-500) were used or in case of CK17, CD26, MHC I, MHC II, CD1a, Ki67, CD4, CD8, IL-8, EDTA buffer pH 9 (Zytomed ZUC 029-500).

Primary antibodies were diluted with DAKO REAL Antibody Diluent.

Antibody	Code	Antigen retrival	Dilution	Incubation °C/time	Description	Source
CK16	ab80574	citrate	1 to 500	20°C/30 min	mouse monoclonal	Abcam
CK17	M7046	EDTA	1 to 100	37°C/45 min	mouse monoclonal	Dako
CD26	ab28340	EDTA	1 to 500	20°C/30 min	rabbit polyclonal	Abcam
Filaggrin	GTX23137	citrate	1 to 100	37°C/45 min	mouse monoclonal	Gene Tex Inc.
TLR4	ab22048	citrate	1 to 200	20°C/60 min	mouse monoclonal	Abcam
MHC I	ab52922	EDTA	1 to 1250	37°C/45 min	rabbit monoclonal	Abcam
MHC II	ab55152	EDTA	1 to 1200	37°C/45 min	mouse monoclonal	Abcam
CD1a	NCL-CD1a-220	EDTA	1 to 15	37°C/45 min	mouse monoclonal	Leica Biosystems
Ki67	M724001	EDTA	1 to 100	37°C/45 min	mouse monoclonal	Dako
CD4	AM421-5M	EDTA	Pure	37°C/45 min	mouse monoclonal	Bio Genex
CD8	N159230	EDTA	Pure	37°C/45 min	mouse monoclonal	Dako
IL-8	MAB208	EDTA	1 to 200	4°C/overnight	mouse monoclonal	R&D Systems
IL-17	ab79056	citrate	1 to 300	4°C/overnight	rabbit polyclonal	Abcam
IL-23	ab115759	citrate	1 to 500	37°C/45 min	rabbit polyclonal	Abcam
IL-31	ab37157	citrate	1 to 300	37°C/45 min	rabbit polyclonal	Abcam

Table 1. Characteristics of antibodies.

Characteristics of primary antibodies as well as their dilution, incubation -time and -temperature are summarised in the Table 1.

Subsequent sections underwent the detection of primary antibodies followed through the secondary antibodies Streptavidin/ Biotin Systems (Zytomed Systems AP 125).

2.6 Analysis of immunochemistry

According to the literature [36], we distinguished normal-, linear-, dotted- and checkered filaggrin patterns. A “normal” pattern was considered if there was a strong staining including 3-4 cell layers of stratum granulosum. Similar, but thinner staining was evaluated as a “linear” pattern. If there was an alternating positive and almost negative filaggrin expression it was described as “checkerboard-like" pattern. By most marked reduction of filaggrin it was estimated as a “dotted” pattern. The proportion of the stained cells were measured separately in stratum corneum, stratum granulosum and stratum spinosum as followed: 0: no stained cells, 1: less than 25% stained cells, 2: between 25- and 50% stained cells and for 3: more than 50% stained cells.

To assess epidermal staining of CK16, CK17, CD26, TLR4, IL-8, and MHC I, we used a semi-quantitative way of immunohistochemical evaluation presented by Chaiyarit et al. [37]. The epidermis was divided into three layers: basal, suprabasal (lower portion of prickle cell layer) and superficial (upper portion of prickle cell layer and stratum granulosum). Each layer was separately evaluated for the staining intensity and the proportion of immunoreactive cells. Intensity of staining was as followed: 0= negative, 1= light, 2= moderate, 3= intense. The proportion of stained cells was graded as 0= if no stained cells, as 1 if there were less than 25% stained cells, as 2 if the stained cells were between 25- and 50% and 3 if there were more than 50% stained cells. To provide an immunostaining- intensity distribution (IID) index, the score of the staining intensity of every layer was multiplied by the score of the proportion of stained cells in that layer. IL-8 was measured as already followed for basal, suprabasal, superficial layers and with the additional division of stratum corneum from superficial layer.

Dendritic cells (CD1a), CD4- and CD8- positive lymphocytes, MHC I- and MHC II- positive cells were semi-quantitatively evaluated by counting the number of positive cells in the skin in 3 consecutive high-power fields (HPF), separately in epidermis and in the upper half of dermis.

IL-17, IL-23 and Il-31 were semi-quantitatively evaluated by counting the number of positive cells in the skin in 3 consecutive high-power fields (HPF) in dermis (in case of IL-17 separately in the upper and in the lower half of dermis).

Ki67 positive cells were counted under 10-fold magnification at the length of 10 mm in the whole epidermis and separately within: basal-, suprabasal- and superficial layer.

2.7 Statistics

The statistical analysis was carried out by the Institute for Biometry and Medical Informatics at the Otto-von-Guericke University of Magdeburg. The analyses were done with the software IBM SPSS Statistics, Version 19 or 21. The outcome variables are described by their

frequencies or means and standard deviations in the different groups. Group comparisons of outcome variables were performed with chi-square tests or Mann-Whitney U tests, depending on the characteristic scale.

P-values were considered as followed: >0.1 no significance ns, ≤ 0.1 tendency (*), ≤ 0.05 significance *, ≤ 0.01 high significance **, ≤ 0.001 highest significance ***.

2.8 Summary

Different procedures, including allergic tests, preparation of tissue samples as well as performance of immunohistologic stains with established and experimental antibodies were described in detail.

Finally, precise methodology for quantitative comparison of histological and immunohistological stains was characterised. Tests used for statistical evaluation are explained in the conclusion.

The results and their analysis will be presented in the following chapters.

3. Clinics and allergy tests

Clinical diagnosis of palmoplantar skin changes, especially by isolated involvement, remains difficult in many cases. Detailed clinical investigation of the whole skin and its derivatives may allow better classification. Allergy tests are necessary for etiological classification of heterogeneous diseases, such as contact dermatitis.

3.1 Results

3.1.1 Clinics

59 patients out of 142 were finally selected: 30 patients with „eczema in psoriatico“, 13 patients with contact dermatitis, 12 with psoriasis and 4 patients with healthy skin as a control group. Selection was made after blind evaluation by two dermatopathologists, who were in accordance with the histological diagnosis.

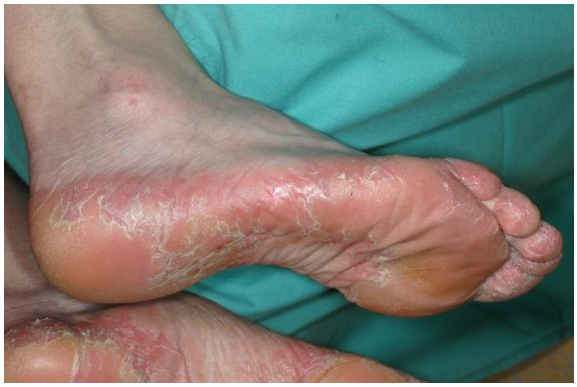

Figure 9. “Eczema in psoriatico” with sharply demarcated erythematous plaques and slight scaling.

In the psoriasis group, there were 9 women and 3 men, with a mean age of 55 years (range 38-84 years). Among the patients with contact dermatitis, there were 5 women and 8 men, with a mean age of 47 years (range 29-75 years). The largest group with “eczema in psoriatico” consisted of 20 women and 10 men with a mean age of 45 years (range 18-74 years). The control group (with healthy skin) included 4 patients- 3 women and 1 man with a mean age of 56 years (range 31-80 years).

In 54%, biopsies were taken from palms (58% of “eczema in psoriatico”, 46% of contact dermatitis, 75% of psoriasis) and in 46% from soles (42% of “eczema in psoriatico”, 54% of contact dermatitis, 25% of psoriasis and in 100% of healthy skin samples).

Some limitation of the study was due to retrospective analysis of clinical manifestations with the help of patients’ records.

Most of the patients in the group of contact dermatitis and “eczema in psoriatico” have an isolated palmoplantar involvement. Clinical manifestation in other localisation was rarely observed. Skin changes at integument were seen in 23.3% in both: contact dermatitis and in

"eczema in psoriatico". Scalp and nail involvement was observed only in "eczema in psoriatico" (each one in 3.3%). In comparison, well-demarcated plaques with erythema and desquamation at the palms and/or soles were the only skin findings in 33.3% of patients with psoriasis. 66.6% of psoriasis-patients had other skin changes: 50% at integument, 8.3% at scalp and 25% at the nails.

Detailed data presenting clinical manifestation in contact dermatitis, psoriasis and in "eczema in psoriatico" is illustrated in Table 2.

A clinical picture of "eczema in psoriatico" with sharp-demarcated erythematous plaques with slight scaling and fissuring is presented in Figure 9.

Clinical manifestation	Contact dermatitis e n=13	Psoriasis p n=9	"Eczema in psoriatico" ep n=30
Palmoplantar (isolated)	76.9%	33.3%	76.7%
integument:	23.1%	50%	23.3%
scalp:	0%	8.3%	3.3%
nails:	0%	25%	3.3%

Table 2. Clinical manifestation in contact dermatitis, psoriasis and "eczema in psoriatico".

3.1.2 Patch-tests

Patch tests turned out to be positive (≥ +) in all patients with contact dermatitis and "eczema in psoriatico" and in 55.6% of examined patients with psoriasis (5/9), as shown in Table 3. Frequency of type-IV sensitisation in the group of contact dermatitis and "eczema in psoriatico" was statistically higher than in the group of psoriasis (in both cases $p \leq 0.01$). There were no statistical changes in the frequency of positive patch-test between contact dermatitis and "eczema in psoriatico". Psoriasis patients with a weak patch-test reaction, did not show any clinical or histological correlate with contact hypersensitivity.

Multiple type IV- sensitisations occurred more often than single type IV sensitisation and were observed in 69.2% of patients with contact dermatitis, 63.3% of patients with "eczema in psoriatico" and in all psoriasis patients with positive patch-tests.

Strong positive test reactions (≥ ++/+++) were seen in 69.2% of patients with contact dermatitis and in 63.3% of patients with "eczema in psoriatico" and in no patients with psoriasis. Strong positive-patch results were most often single; the ratio single versus multiple strong type IV- sensitisations were as followed: 5: 3 in a group of contact dermatitis and 4: 3 in the group of "eczema in psoriatico".

The most common positive allergen was nickel sulfate (34.6% of all examined patients), followed by potassium dichromate and balsam of Peru (both 21.2%), cobalt chloride (19.2%), fragrance-mix I+II (15.7%) and formaldehyde (11.8%). Detailed analysis of the frequency of

the most common allergens is presented in Table 4.

Allergies to nickel, cobalt, fragrances and balsam of Peru were observed mostly in women.

Illness	Contact dermatitis e n=13	Psoriasis p n=9	"Eczema in psoriatico" ep n=30
Type IV sensitisation (≥+):	100%	55.6%	100%
Type IV sensitisation (≥++):	69.2%	0%	63.3%
Single vs. multiple sensitisation (≥+):	4: 9	0: 5	9: 21
Single vs. multiple sensitisation (≥++):	5: 3	0: 0	4: 3

Table 3. Frequency of type IV sensitisation in contact dermatitis, psoriasis and in "eczema in psoriatico".

Conversely, men were more often affected by an allergy to potassium dichromate and to formaldehyde. The sex ratio (women to men) in the groups allergic to following substances was as follows: 14: 3 for nickel sulfate; 5: 6 for potassium dichromate; 8: 3 for balsam of Peru; 6: 4 for cobalt chloride; 6: 1 for fragrances and 2: 4 for formaldehyde.

Strong, positive reactions (≥ ++/+++) were seen accordingly in 23.1% of all examined patients for nickel sulfate, in 15.4% for potassium dichromate, in 9.8% of all examined patients for cobalt chloride and formaldehyde and only in 2% patients for balsam of Peru.

In the group of contact dermatitis, the most common allergen was formaldehyde. Positive reactions were strong (≥ ++/+++) in all of cases, and occurred in 30.7% of patients, affecting mostly men (75%). The second most common allergens in the group of contact dermatitis were nickel sulfate and potassium dichromate, with positive reactions in 15.4% of patients.

In the group of "eczema in psoriatico", the most common allergen was nickel sulfate. Every second patient (50%) showed a patch-positive reaction and every third (33.3%) a strong patch-positive reaction. The second most common allergen in the group of "eczema in psoriatico" was potassium dichromate, with 30% of allergy occurrence (and 23.3% with strong patch-positive reactions). The third most common allergens were cobalt chloride and balsam of Peru: in both cases, 23.3% of patients showed positive reactions (accordingly 16.7% and 3.3% of patients with strong reactions). In the group of "eczema in psoriatico" only 6.7% of patients were allergic to formaldehyde (3.3% suffered from a strong reaction).

In the group of psoriasis, there were only weak positive allergens. Type-IV sensitisation to thiuram mix, balsam of Peru und cosmetics (40% each) were more often than sensitisation to nickel sulfate, fragrance-mix, cobalt chloride and colophonium (20% each).

Contact allergens	Contact dermatitis e n=13	Psoriasis p n=9	"Eczema in psoriatico" ep n=30
Nickel sulfate:			
≥ +	15.4%	11.1%	50%
≥ ++	15.4%	0%	33.3%
Potassium dichromate:			
≥ +	15.4%	0%	30%
≥ ++	7.7%	0%	23.3%
Balsam of Peru:			
≥ +	15.4%	22.2%	23.3%
≥ ++	0%	0%	3.3%
Cobalt chloride:			
≥ +	15.4%	11.1%	23.3%
≥ ++	0%	0%	16.7%
Fragrance-mix I+II:			
≥ +	15.4%	11.1%	16.7%
≥ ++	7.7%	0%	6.7%
Formaldehyde:			
≥ +	30.7%	0%	6.7%
≥ ++	30.7%	0%	3.3%

Table 4. The most common allergens and their frequency in contact dermatitis, psoriasis and in "eczema in psoriatico".

3.1.3 IgE in serum

Presence of IgE in serum was checked in 11 patients with contact dermatitis, in 5 patients with psoriasis and in 21 patients with "eczema in psoriatico". The results are shown in Table 5.

IgE turned out to be in normal range in 81.8% patients with contact dermatitis, 60% with psoriasis and in only 23.8% of patients with "eczema in psoriatico".

Slightly elevated IgE levels in serum were detected in 18.2% of patients with contact dermatitis, in 20% of examined patients with psoriasis, and in 52.4% of examined patients with "eczema in psoriatico". Moderately- and strongly elevated IgE values were found in accordingly 9.5 and 14.3% of patients with "eczema in psoriatico" and in one patient with psoriasis (20%).

IgE in serum	Contact dermatitis e n=11	Psoriasis p n=5	"Eczema in psoriatico" ep n=21
Negative (<100):	81.8.%	60%	23.8%
Positive (>100)	18.2%	40%	76.2%
Slight elevated (100-500):	18.2%	20%	52.4%
Moderate elevated (500-1000):	0%	0%	9.5%
Strong elevated (>1000):	0%	20%	14.3%

Table 5. IgE values in serum of patients with contact dermatitis, psoriasis and "eczema in psoriatico".

3.2 Discussion

3.2.1 Clinics

Patients dealing with sharply demarcated scaling erythema on hands and feet should be examined carefully. The existence of other skin changes may facilitate the clinical diagnosis. Just single, sharply demarcated erythrosquamous plaques, for example on elbows and knees, or erythema with fissuring in the anal cleft, erythematous plaques with scaling on scalp, oil spots or onycholysis can help to diagnose psoriasis. Positive history of arthritis affecting terminal joints of the fingers and toes, spondylitis, sacroilitis, tendinitis can assist the diagnosis of psoriatic arthritis.

On the other hand, pruritic papular- and vesicular- eruptions on erythematous ground or lichenification, non-sharply demarcated erythematous plaques with slight scaling, fissures and excoriations are characteristic for contact dermatitis.

Nail pitting, it can occur in both psoriasis and eczema. Isolated scaling on the scalp may be a manifestation of pityriasis capitis.

Positive history of psoriasis does not exclude coexistence of contact dermatitis or atopy or irritation. Hands and feet are exposed to different mechanical and environmental factors. The detailed diagnostic inclusive patch testing is essential for right diagnosis and successful treatment.

In the examined group of "eczema in psoriatico" and allergic chronic contact dermatitis, over 70% of patients had isolated palmoplantar skin changes. Isolated palmoplantar lesions were also found in every third examined patient with psoriasis. Clinical diagnosis by isolated skin

changes remains difficult in many cases. In our study, the final diagnosis was based on clinics, histologic patterns and results of allergy tests as well as on past medical history.

3.2.2 Patch-tests

Our study was retrospective; a detailed evaluation of clinical significance of type IV sensitisation was limited.

One of the inclusion criteria in the group of contact dermatitis and "eczema in psoriatico" was at least one positive reaction in the patch test. This is why the frequency of sensitisation to different allergens in our patients was higher compared to the data found in the literature. Cases with chronic irritant contact dermatitis and irritant "eczema in psoriatico" without contact sensitisation were excluded from this study and examined separately.

37 of 59 examined patients were women. Only in the group of contact dermatitis, there was the predominance of men over women (8: 5). The sex ratio may have been influenced, due to different occupational- and domestic factors, the frequency of positive patch-test reactions in groups of "eczema in psoriatico", contact dermatitis and psoriasis.

According to the literature, the most common contact allergens are nickel, fragrances and thiomersal [6,38]. In our study, sensitisation to metals (nickel, chromate, cobalt), as well as to balsam of Peru, fragrances and formaldehyde were observed most often. There were some differences in the frequency of positive patch tests in groups of "eczema in psoriatico", contact dermatitis and psoriasis.

Nickel is the most common allergen. Estimated incidence of nickel allergy accounts for about 8.6% among the whole population [6] and between 20 and 30% among patch tested patients [39]. Due to an increased exposure to nickel-releasing jewellery and to wet works, women are affected by nickel allergy 3-10 more frequently than men [6]. In our study, type IV sensitisation to nickel was found in 34.6% of all examined patients (14 women and 2 men), accordingly in 50% with "eczema in psoriatico", 15.4% with contact dermatitis and 11.1% with psoriasis. These differences can probably be connected with the sex ratio (the group of "eczema in psoriatico" was represented mostly by women and of contact dermatitis mostly by men). Nickel sensitisation occurred in 68.75% as multiple allergies, usually with other metals. Nickel allergy may cause or trigger hand eczema by different pathogenic mechanisms [39], especially in women [40]. Hand eczema due to nickel sensitisation can result from occupational or domestic exposure, or be part of systemic allergic contact dermatitis[39] . Skin barrier diseases due to filaggrin-loss-of-function mutations may be also an important endogenous factor related to sensitisation to nickel [41].

The chromate allergy is estimated between 3.1 and 10.5% [42]. In our study, 21.6% of all patients had positive patch tests to potassium dichromate. Chromate allergy can be acquired due to the occupational exposure, especially in the building and machine industry. Although cement is the most common source of chromate allergy, its frequency is decreasing due to

legislation regulating the concentration of hexavalent chromate in ready-to-use cement (in Denmark since 1981, in the EU since 2003)[42]. Due to this legislation, the sex ratio of the chromate allergy is changing. For example, the chromate allergy in Denmark is nowadays more often observed in women than in men, possibly due to chrome-tanned leather in gloves and shoes [42]. In our study, chromate sensitisation was observed in 6 men and in 5 women, in all cases as multiple allergies. In 8 of 11 patients allergic to potassium dichromate, there was, probably due to occupational exposures, contemporary sensitisation to nickel and/or cobalt. The average age of patients with chromate allergy was 42.7 (18 to 60 years). Chromate allergy was observed in 30% patients with "eczema in psoriatico" mostly as co-sensitisation to other metals and in 15.4% patients with contact dermatitis. Chromate allergy is of clinically significance and can trigger or cause therapy-resistant hand- and foot eczema.

Cobalt is used in manufacturing alloys. The coexistence of a nickel- and cobalt allergy can be explained by the occurrence of both metals in nature [43]. The frequency of cobalt allergy was estimated between 1-3% of adults. In our study, positive patch tests to cobalt were observed in 19.2% of examined patients; 4 men and in 6 women with an average age of 38.9 years (from 21 to 74 years). Cobalt sensitisation was diagnosed more often in "eczema in psoriatico" (23.3%) than in contact dermatitis (15.4%) or psoriasis (11%). Cobalt allergy occurred in our cases often in association with a positive test to nickel sulfate (60%) or potassium dichromate (50%) or to both of them (40%).

Formaldehyde is used as disinfectant and preservative agent in the food- and metal working industry, as well as a disinfectant in medical sector. Formaldehyde belongs to clinically significant allergens in occupational hand eczema. In Germany, 2% of patch tested patients with contact dermatitis showed an allergy to formaldehyde. In comparison, the sensitisation rate to formaldehyde in USA and Canada is higher and estimated between 5 and 10% [44]. Sensitisation to formaldehyde was observed in 11.7% of our patients. Surprisingly, formaldehyde turned out to be the most common allergen in the group of contact dermatitis affecting 30.7% of patients, in 75% of men.
Sensitisation to balsam of Peru (which may indicate fragrance allergy) and to fragrances was observed accordingly in 21.6% and 15.7% of all examined patients and was rarely strong (accordingly 2% and 5.7%). Allergy to fragrances and balsam of Peru develops often in course of chronic diseases due to application of various "ointments" with sensitising potential.

There are conflicting results between correlation of psoriasis and contact sensitivity. Bansgaard et al. observed an inverse relationship between psoriasis and contact allergy [45]. The results based on register study with 15461 patch-tested patients (806 patients of 15461 suffered from psoriasis). The authors did not evaluate the influence of the site of lesions or the disease's duration. Moss et al. [46] showed, that patients with psoriasis were less responsive to sensitisation with DNCB than healthy controls. On the other hand, other authors reported higher incidence of type IV sensitisation in palmoplantar psoriasis than in psoriasis

without palmoplantar involvement [47]. For example, Caca-Biljanovska et al. observed positive-patch tests in 39.5% of 38 patients with palmoplantar psoriasis versus 12.7% of 63 patients with psoriasis vulgaris without palmoplantar localisation [48]. In some other studies, there were no differences between the frequencies of type IV sensitisation in psoriasis patients due to the site of lesions. In the group of 305 patients with psoriasis examined by Barille et al. [49], 24% showed at least one positive patch-tests reaction, of which 22.4% of 80 patients with palmoplantar involvement. Malhotrat et al. [50] examined 200 patients with psoriasis. At least one positive patch-test reaction was observed in 21.6% of them. The frequency of positive patch tests correlated with the disease's duration. In this study, the site of lesions did not show any relationship with the positivity of patch-tests. Patch-test positivity was observed mostly in cases of topical medicaments or fragrances.

We believe that patch-testing is mandatory in all cases with palmoplantar psoriasis. In our study, there were only 9 patch test- examined patients with psoriasis. Every second showed weak positive reaction without clinic and histological changes characteristic for eczema. It can be speculated, that in the predisposed patients with psoriasis type IV sensitisation can lead to additional development of contact dermatitis, which we call “eczema in psoriatico”.

3.2.3 IgE levels in serum

Atopy is known to be an important risk factor for the development and maintenance of chronic hand eczema. The elevated total IgE levels in serum have a positive predictive value for diagnosis of atopy.

Inflammation seen in atopic disorders is determined by type 2 Th cells in contrary to psoriasis which is determined by Th-17 and Th-1 cells. Both Th-1 and Th-2 T cells are assumed to antagonise each other on a cytokine level [51,52]. Patients with Th-1 mediated diseases were found to have a lower prevalence of atopy [53]. A recent study of Hajdarbegovic et al. [54] of 448 patients, confirmed a reduced prevalence of atopic disorders only in the case of psoriatic arthritis but not in psoriasis vulgaris.

Measurement of IgE levels in serum was performed in 37 of 59 patients. The results were collected from the medical records of examined patients. Due to the retrospective aspect of our study, detailed evaluation of self-reported symptomatology of atopic disorders (ie, hay fever, asthma) was limited.

Patients with “eczema in psoriatico” showed a higher frequency of elevated IgE levels in serum compared to patients with contact dermatitis and psoriasis. It can be concluded that patients with psoriasis with coexisting atopy can develop easier contact sensitisation and in consequence “eczema in psoriatico”. The role of atopy in the developing of “eczema in psoriatico” needs further clarification.

3.3 Summary

Clinical diagnosis remains difficult by isolated palmoplantar involvement. This chapter has given an overview of the differences in clinical manifestations between contact dermatitis, psoriasis and “eczema in psoriatico”. The frequency of contact sensitisation and detailed analysis of the most frequent allergens in all three groups have been studied precisely. The potential role of atopy is discussed at the end of the chapter.

4. Histology

Histological differentiation between psoriasis and chronic contact dermatitis in palmoplantar localisation may be troublesome. Distinguishing a new entity “eczema in psoriatico” allows a better histological classification. The first part of this chapter comprises of the description of histological features found in contact dermatitis, psoriasis and in “eczema in psoriatico” and the second, their detailed analyses.

4.1 Results histology

The frequency of different histological features in contact dermatitis, psoriasis, “eczema in psoriatico” and in healthy skin are shown in Table 6 and 7.

In the grade of parakeratosis, there were statistical differences between contact dermatitis and psoriasis and between contact dermatitis and “eczema in psoriatico”. Mild parakeratosis was a common feature in contact dermatitis 85% (11/13) and was less often seen in psoriasis and “eczema in psoriatico”-in both groups in 33%. Moderate and heavy parakeratosis were more often in psoriasis (accordingly 25% and 42%) and in “eczema in psoriatico” (accordingly 36% and 30%) and not seen in contact dermatitis.

Multiple foci of parakeratosis were found to be more common in contact dermatitis 77% (10/13) than in “eczema in psoriatico” 33% (11/33) and were not found in psoriasis 0% (0). Vertically distributed parakerathosis and orthokeratosis were more often seen in psoriasis patients 58% (7/12) than in “eczema in psoriatico” 15% (5/33) and were not observed in contact dermatitis 0% (0). Confluent parakeratosis was more common in “eczema in psoriatico” 52% (17/33) and in psoriasis 42% (5/12) and was rarely observed in contact dermatitis 8% (1/13).

A typical histological characteristic of psoriasis was neutrophils found in parakeratosis 92% (11/12), rarely observed in “eczema in psoriatico” 15% (5/33) and in contact dermatitis 8% (1/13). Neutrophils and exsudation both occurring in parakeratosis were a common finding in “eczema in psoriatico” 85% (28/33) and in contact dermatitis 62% (8/13) in contrary to psoriasis 8% (1/12). Isolated exsudation in parakeratosis was rarely found in contact dermatitis 15% (2/13) and was not observed in psoriasis and in “eczema in psoriatico”.

There were no statistical differences in grade of acanthosis between psoriasis, contact dermatitis and “eczema in psoriatico”. Most of the slides showed moderate acanthosis- accordingly 77% of contact dermatitis, 83% of psoriasis and 85% of “eczema in psoriatico”.

Regular acanthosis was more frequent in psoriasis 83% (10/12) followed by mixed pattern 17% (2/12). In contrast, irregular acanthosis was found to be more common in contact der-

matitis 69% (9/13). In "eczema in psoriatico" regular acanthosis was found with similar frequency as mixed pattern- accordingly 52 and 48%.

Loss or thinning of the whole granular layer was found more often in psoriasis 42% (5/12) and in "eczema in psoriatico" 33% (11/33) and rarely in contact dermatitis 15% (2/13). Partial loss of the granular layer was seen more often in "eczema in psoriatico" 61% (20/33), followed by psoriasis 33% (4/12) and contact dermatitis 15% (2/13). Thinning of the suprapapillary plates was often observed in psoriasis and in "eczema in psoriatico" accordingly in 67 and in 85%, whereas it was a less common feature in contact dermatitis 8% (1/13).

Isolated club-shaped rete ridges were frequent seen in psoriasis 92% (11/12), less frequent in "eczema in psoriatico" 46% (21/46) and were not seen in contact dermatitis 0% (0). Isolated V-shaped rete ridges was rarely seen and found only in contact dermatitis 8% (1/13). Mixed pattern combining club-shaped and V-shaped rete ridges was dominating in contact dermatitis 92% (12/13) and in "eczema in psoriatico "60% (20/33) in contrary to psoriasis, only 8% (1/12).

Mild spongiosis in the lower part of epidermis was a common finding in healthy palmoplantar skin 80% (4/5), in contrary to "eczema in psoriatico", contact dermatitis and psoriasis- accordingly 18, 23 and 25%. Full-thickness spongiosis was observed in 45% of "eczema in psoriatico" cases (15/33) and in 23% of contact dermatitis, and was not seen in any psoriasis skin samples. Spongiotic vessels were often found in contact dermatitis 54% (7/13), less often in "eczema in psoriatico" 36% (12/33) and were lacking in psoriasis.

Typical finding of contact dermatitis and of "eczema in psoriatico" was lymphocytic exocytosis in epidermis (both 100%) in contrary to psoriasis with only 25% (3/12).

Eosinophiles were rarely seen in "eczema in psoriatico" 12% (4/33) and in contact dermatitis 23% (3/13) and were lacking in psoriasis and in healthy skin.

Tortuous or dilated capillaries in the upper epidermis were typical findings in psoriasis (100%), and were seen less frequently in "eczema in psoriatico" 45% (15/33) and in contact dermatitis 23% (3/13). Horizontal vessels were a frequent finding in contact dermatitis 54% (7/13), whereas it was rarely seen in "eczema in psoriatico": 9% (3/33). Mixed patterns combining tortuous, dilated and horizontal vessels were observed in 45% of "eczema in psoriatico" cases (15/33) and in 23% of contact dermatitis (3/13). Oedema of papillary dermis was present in 67% (8/12) of patients with psoriasis, in 76% (25/33) of patients with "eczema in psoriatico", whereas it was a less common feature in patients with contact dermatitis: 15% (2/13). All slides were negative in PAS staining.

Typical histological features of "eczema in psoriatico" were vertically para- and othokeratosis, parakeratosis with neutrophils and plasma, regular acanthosis, loss of granular layer, thinning of suprapapillary plates, lymphocytic exocytosis and spongiosis, which are presented in Figure 10.

Histologic features	Contact dermatitis e n=13	Psoriasis p n=12	Eczema in psoriatico ep n=33	Healthy skin c n=5	P-value e vs p	P-value ep vs e	P-value ep vs p	P-value ep vs c
Parakeratosis: mild	85%	33%	33%	0%				
moderate	0%	25%	36%	0%	**	***	ns	***
strong	0%	42%	30%	0%				
Parakeratosis: multiple foci	77%	0%	33%	0%				
confluent	8%	42%	52%	0%	***	**	**	***
Para- /orthokeratosis v.	0%	58%	15%	0%				
Parakeratosis: with neutrophils	8%	92%	15%	0%				
with plasma	15%	0%	0%	0%	***	(*)	***	***
neutrophils & plasma	62%	8%	85%	0%				
Acanthosis: mild	23%	0%	6%	80%				
moderate	77%	83%	85%	20%	ns	ns	ns	**
strong	0%	17%	9%	0%				
Acanthosis: regular	0%	83%	52%	0%				
irregular	69%	0%	0%	100%	***	***	(*)	***
mixed	31%	17%	48%	0%				

*Table 6. Histologic features: evaluation of type and grade of parakeratosis and acanthosis. ns nonspecific, (0)>0,1 no significance, (*) ≤ 0.1 tendency, * ≤ 0.05 significance, **≤ 0.01 high significance, ***≤ 0.001 highest significance.*

Histologic features	Contact dermatitis e n=13	Psoriasis p n=12	Eczema in psoriatico ep n=33	Healthy skin c n=5	P-value e vs p	P-value ep vs e	P-value ep vs p	P-value ep vs c
Loss/thinning of granular layer: no	69%	25%	6%	100%				
yes	15%	42%	33%	0%	(*)	***	ns	***
partially	15%	33%	61%	0%				
Thinning of the suprapapillary plates:	8%	67%	85%	0%	**	***	ns	***
Rete ridges: club-shaped	0%	92%	39%	0%				
V-shaped	8%	0%	0%	80%	***	**	**	***
mixed	92%	8%	61%	20%				
Lymphocytic exocytosis in epidermis	100%	25%	100%	0%	***	ns	***	***
Capillary in upper dermis: tortuous/ dilated	23%	100%	45%	0%				
horizontal	54%	0%	9%	40%	***	**	**	(*)
mixed	23%	0%	45%	60%				
Spongiosis: none	0%	75%	0%	20%				
full-thickness	23%	0%	45%	0%				
lower part of epidermis	23%	25%	18%	80%	***	ns	***	***
spongiotic vesicels	54%	0%	36%	0%				
Infiltrate in upper dermis: mild	15%	42%	12%	100%				
moderate	77%	58%	76%	0%	ns	ns	ns	***
strong	8%	0%	12%	0%				
Oedema of the papillary dermis	15%	67%	76%	0%	*	***	ns	*

*Table 7. Histologic features: evaluation of loss/thinning of granular layer, thinning of the suprapapillary plates, form of rete ridges and of capillaries in the upper dermis, lymphocytic exocytosis in epidermis, spongiosis, infiltrate in upper dermis and oedema of the papillary dermis ns nonspecific, (0)>0.1 no significance, (*) ≤ 0.1 tendency, * ≤ 0.05 significance, **≤ 0.01 high significance, ***≤ 0.001 highest significance.*

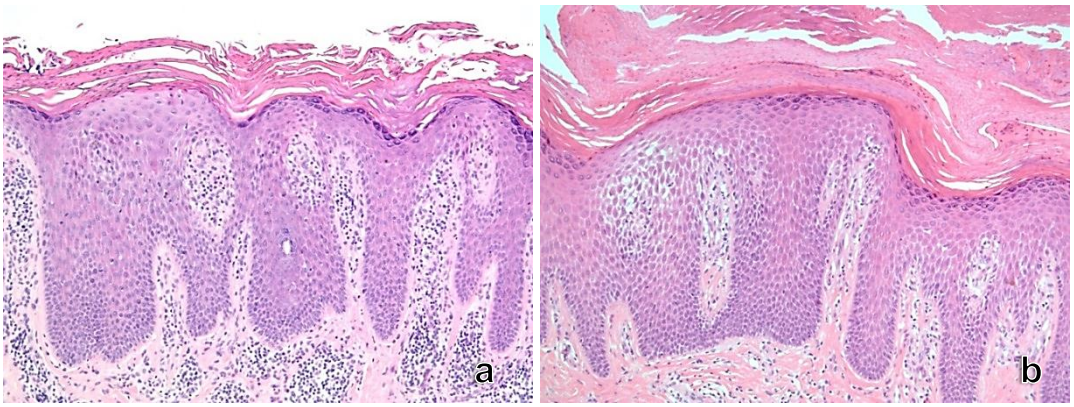

Figure 10. "Eczema in psoriatico" (a and b) with parakeratosis containing both neutrophils and plasma,regular acanthosis, loss of granular layer, thinning of suprapapillary plates, lymphocytic exocytosis and spongiosis.

4.2 Discussion histological results

In the literature, there are a few studies comparing histologic features of non-pustular palmoplantar psoriasis with palmoplantar contact dermatitis [55,56]. It is well known, that histological differential diagnosis between these both diseases in palmoplantar localisations may be troublesome or even impossible.

In our study, distinguishing a new group of patients with the diagnosis of "eczema in psoriatico" (which enclosed patients with overlapping histological features of both psoriasis and contact dermatitis) enabled easier differentiation between typical palmoplantar psoriasis and typical palmoplantar contact dermatitis.

Statistically significant histological features useful in diagnosing of palmoplantar psoriasis were in our study: regular acanthosis ($p \leq 0.001$), club shaped rete ridges ($p \leq 0.001$), thinning of suprapapillary plates ($p \leq 0.01$), neutrophils in parakeratosis ($p \leq 0.001$), tortuous and dilated capillaries in upper dermis ($p \leq 0.001$), oedema of papillary dermis ($p \leq 0.05$) and presence of Munro microabscesses ($p \leq 0.001$). Loss or thinning of granular layer, known to be typical for psoriasis, was more frequent in psoriasis than in contact dermatitis, but occurred only partially in many cases.

The features helpful for diagnosis of palmoplantar contact dermatitis were in our cases: irregular acanthosis ($p \leq 0.001$), multiple foci of parakeratosis ($p \leq 0.001$), lymphocytic exocytosis in epidermis ($p \leq 0.001$) and horizontal vessels in upper dermis. Full-thickness spongiosis and spongiotic vesicels were also considered in favour of contact dermatitis. Isolated plasma exsudation in parakeratosis was rarely observed (15%) and in most of the cases (62%) occurred in combination with neutrophils. Isolated V-shaped rete ridges, known to be typical for contact dermatitis, were not a common finding in our cases in contrary to mixed patterns combining club-shaped- and V-shaped- rete ridges.

"Eczema in psoriatico" showed overlapping histological features with both psoriasis and contact dermatitis. The following histological findings of "eczema in psoriatico" were shared

with psoriasis: moderate to strong parakeratosis, regular acanthosis, loss or thinning (also partially) of granular layer, thinning of suprapapillary plates, oedema of papillary dermis and presence of Munro microabscesses. The following features of "eczema in psoriatico" were shared with contact dermatitis: neutrophils and plasma exsudation in parakeratosis, lymphocytic exocytosis in epidermis, full-thickness spongiosis or formations of spongiotic vessels.

Parakeratosis and orthokeratosis vertically distributed were typical for psoriasis, absent in contact dermatitis, but rarely seen in "eczema in psoriatico" (15%). Rete ridges in "eczema in psoriatico" differed from both psoriasis and contact dermatitis showing mixed patterns (61%) or isolated club-shaped patterns (39%). Capillaries in upper dermis showed with the same frequency tortous/ dilatated shape or mixed pattern combining tortous/ dilatated- and horizontal- vessels. Eosinophiles in upper dermis were a rare histological feature observed only in contact dermatitis and in "eczema in psoriatico" and showed no statistical significance. Grade of acanthosis and of infiltrate in upper dermis also showed no statistical differences between psoriasis, contact dermatitis and "eczema in psoriatico" in palmoplantar localisation.

Similar to previous observations [47,55], we detected spongiosis in some psoriasis samples. In contrary to other studies, (Aydin et al. [55]: spongiotic vesicles in 76.5% of examined palmoplantar psoriasis), we observed in every fourth patient with psoriasis, mild spongiosis located in lower part of epidermis. Surprisingly, this finding was also noticed in 80% of healthy skin samples.

4.3 Summary

Histological evaluation of palmoplantar lesions was a relevant part of this study. The first section focused on the analysis and quantitative comparison of histological parameters that were considered helpful in the diagnosis of psoriasis and contact dermatitis.

According to our results, which are discussed in the second section, it was possible to distinguish distinctive patterns characteristics for contact dermatitis, psoriasis or "eczema in psoriatico" just in H&E stains. "Eczema in psoriatico" showed overlapping histological features with both psoriasis and contact dermatitis.

5. Immunohistology

For a better understanding of pathomechanism of “eczema in psoriatico”, different immunohistological stainings were performed. We focused on alternations in epidermal differentiation, acquired and innate immunity.

5.1 Results immunohistology

5.1.1 Filaggrin

The frequency of different filaggrin patterns varied in all diseases from one another. As expected, healthy skin controls showed a strong filaggrin staining with the positivity of 3-4 layers of stratum granulosum.

“Eczema in psoriatico” had the most reduced filaggrin expression with accordingly 42.4% of “dotted”-, 33.3% of “checkered”-, 21.2% of “linear”- and only 3% per cent of “normal”- staining. In the psoriasis group, a down-regulated filaggrin expression was less prominent, with accordingly 50% of “linear”- and 25% of “checkered”- and 16.7% of “normal” staining. In the group of contact dermatitis, the filaggrin alterations were only slightly reduced: the “linear“pattern (46.2%) was followed by “normal” staining (38.5%). Distribution of filaggrin patterns in “eczema in psoriatico”, contact dermatitis, psoriasis and in healthy skin are presented in Figures 11 and 12. The evaluation of distribution of filaggrin patterns in patients

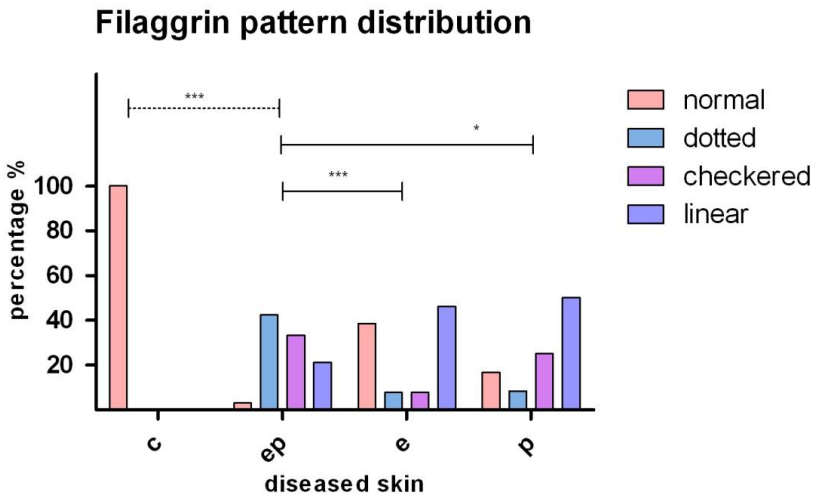

Figure 11. Filaggrin patterns distribution in “eczema in psoriatico” (ep) contact dermatitis (e), psoriasis (p) and in healthy skin (c).

without elevated IgE in serum did not reveal any significant differences in comparison to foregoing assessment. In those cases, “eczema in psoriatico” also turned out to have the most reduced filaggrin expression compared to contact dermatitis ($p \leq 0.01$) and psoriasis ($p \leq 0.5$).

There were no statistical differences between psoriasis and contact dermatitis.

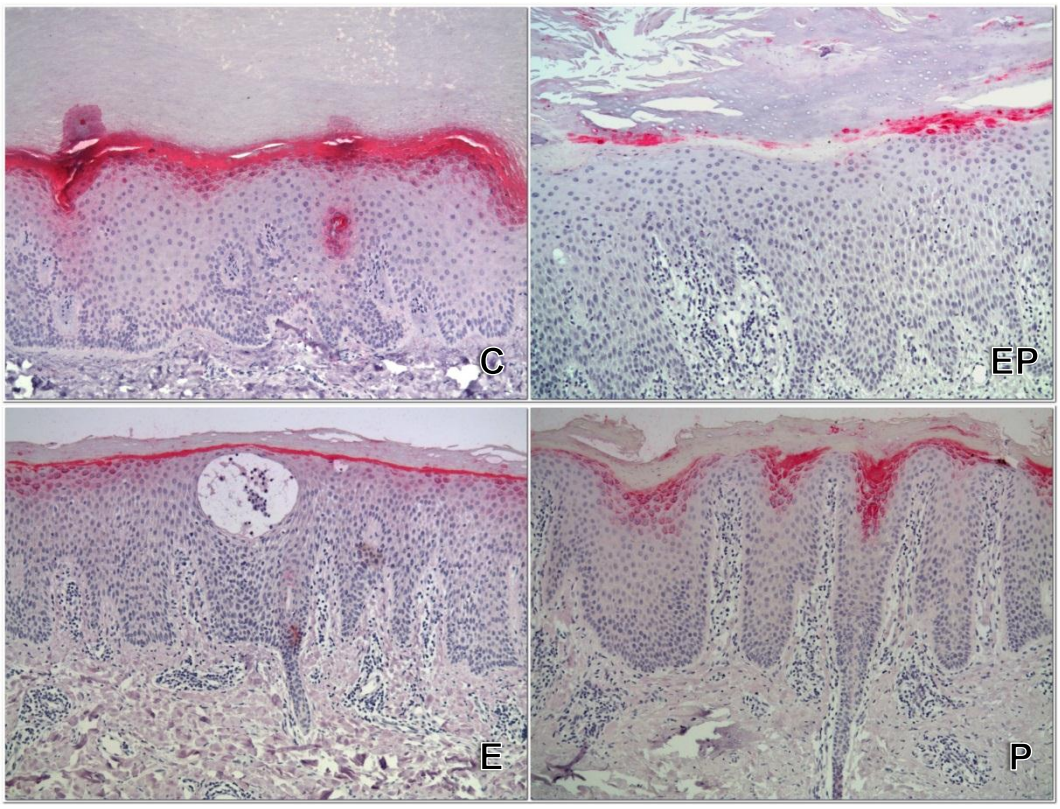

Figure 12. Filaggrin patterns: "dotted" in "eczema in psoriatico" (ep)," linear" in contact dermatitis (e), "checkered" in psoriasis (p) and "normal" in healthy skin (c).

The evaluation of proportion of the positive stained cells showed statistically differences in stratum spinosum (Figure 13). Psoriasis turned out to have more positive stained cells as "eczema in psoriatico" (p≤0.01) and allergic contact dermatitis (p≤0.5).

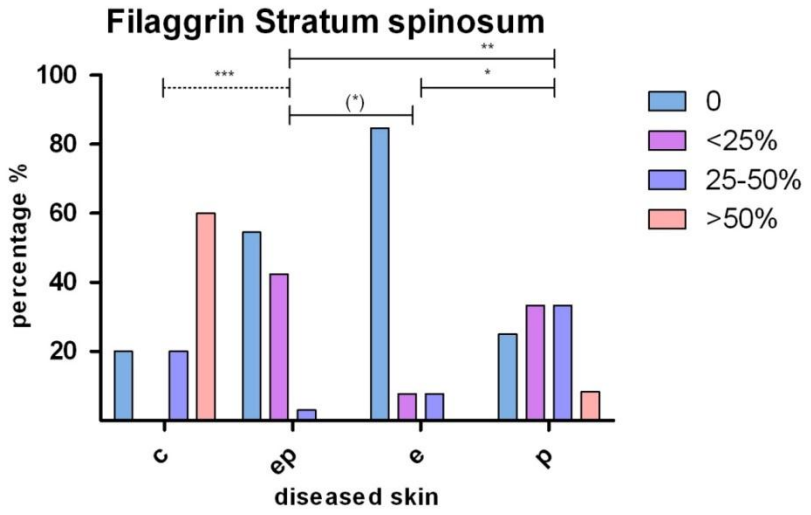

Figure 13. Filaggrin staining within stratum spinosum in "eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p) and in healthy controls (c).

5.1.2 Cytokeratines 16 and 17 (CK16, CK17)

As presented in Figure 14 and 15, positive CK16 staining with diffuse patterns was observed in suprabasal- and superficial- epidermis layers of all examined inflammatory diseases (ep, e, p) and was absent in healthy skin (c). There were no statistical differences between psoriasis, contact dermatitis and "eczema in psoriatico" (all three similarly highly positive) in contrary to healthy skin samples (negative staining with except to positive acrosyryngium) ($p \leq 0.001$).

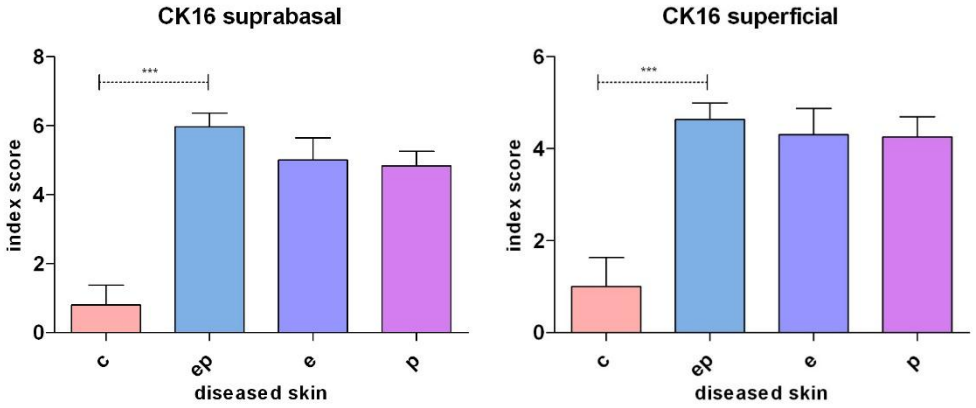

Figure 14. CK16 in "eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p), and in healthy skin (c), accordingly in suprabasal- and superficial layers .

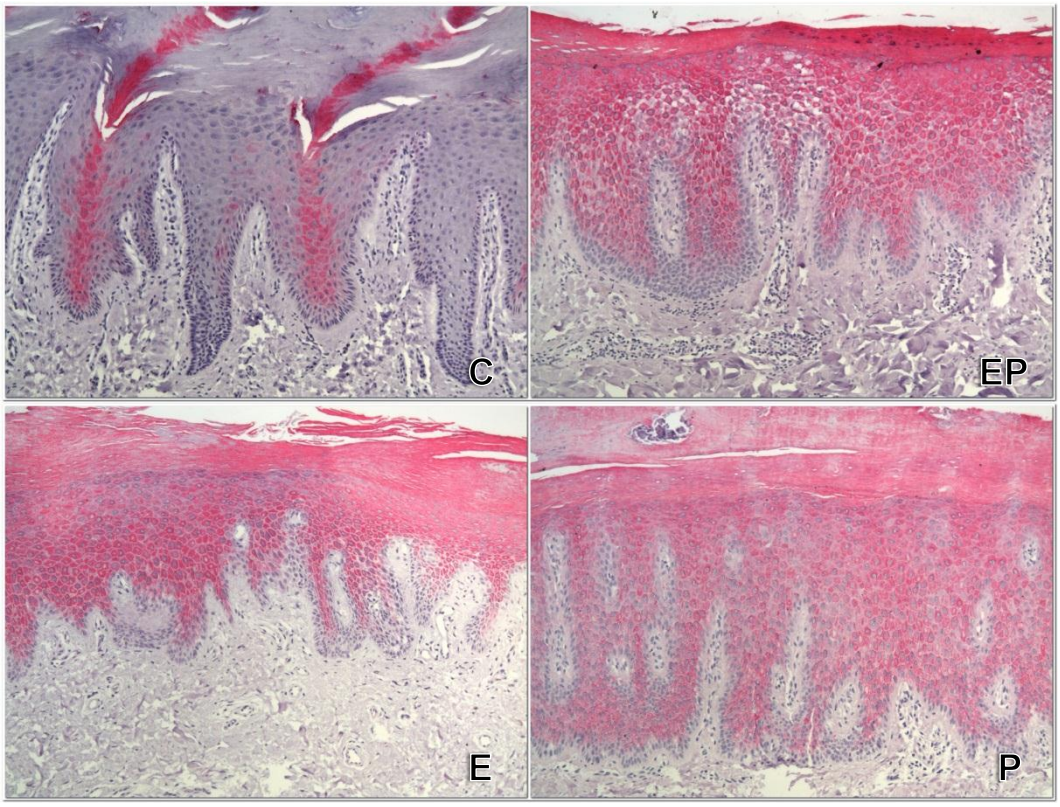

Figure 15. CK16 in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

CK17 staining was found to be negative in basal- and positive in suprabasal- and in superficial- epidermis layers of all examined inflammatory diseases (ep, e, p). Healthy controls (c) showed negative staining in the whole epidermis. Strong positive reactions were observed in "eczema in psoriatico" and psoriasis in upper suprabasal- and in superficial- layers in contrary to weak positive staining in contact dermatitis (accordingly $p \leq 0.01$ in suprabasal layer, $p \leq 0.001$ in superficial layer comparing "eczema in psoriatico" and contact dermatitis). There were no statistical differences between "eczema in psoriatico" and psoriasis. All results are illustrated in Figure 16 and 17.

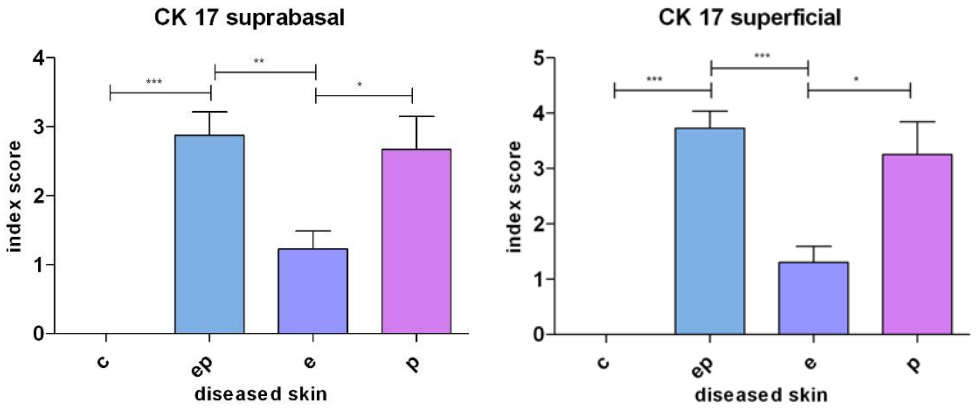

Figure 16. CK17 in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c) in suprabasal- und superficial layers.

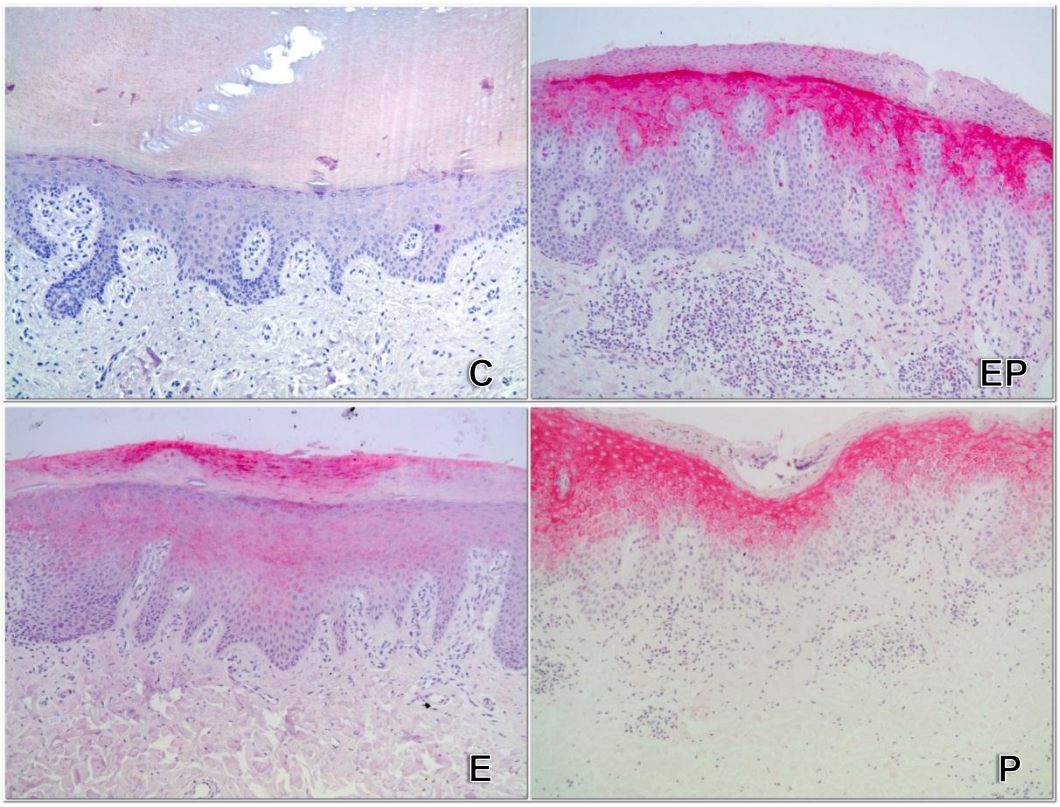

Figure 17. CK17 in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.3 Dipeptidyl peptidase IV (CD26)

CD26 staining showed a positive reaction in the whole epidermis of all examined inflammatory diseases, as presented in Figure 18 and 19. In health controls, weak positive reactions were observed in basal- and suprabasal layers. There were no statistical differences between "eczema in psoriatico", allergic contact dermatitis and psoriasis in basal keratinocytes (all slides showed up-regulated CD26 expression compared to healthy controls). Psoriasis slides had stronger staining compared to "eczema in psoriatico" in suprabasal- ($p \leq 0.05$) and superficial layers ($p \leq 0.01$). There were no statistical differences in the CD26 staining between "eczema in psoriatico" and allergic contact dermatitis.

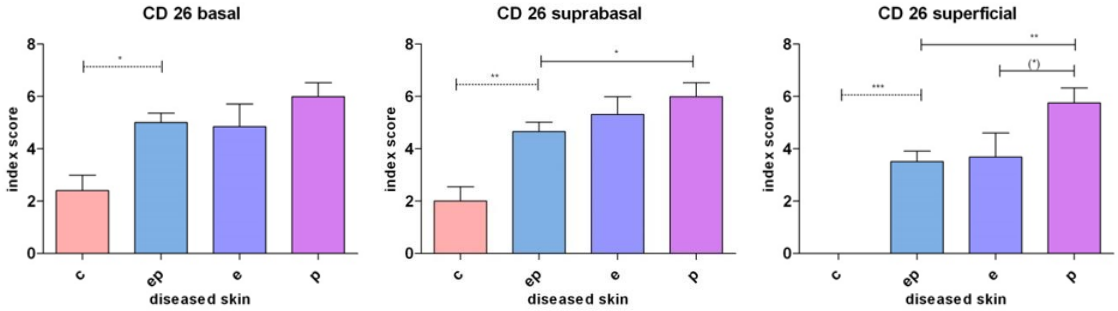

Figure 18. CD26 with overexpressed staining in suprabasal- and superficial layers of psoriasis (p) compared to contact dermatitis (e),"eczema in psoriatico"(ep) and healthy skin (c).

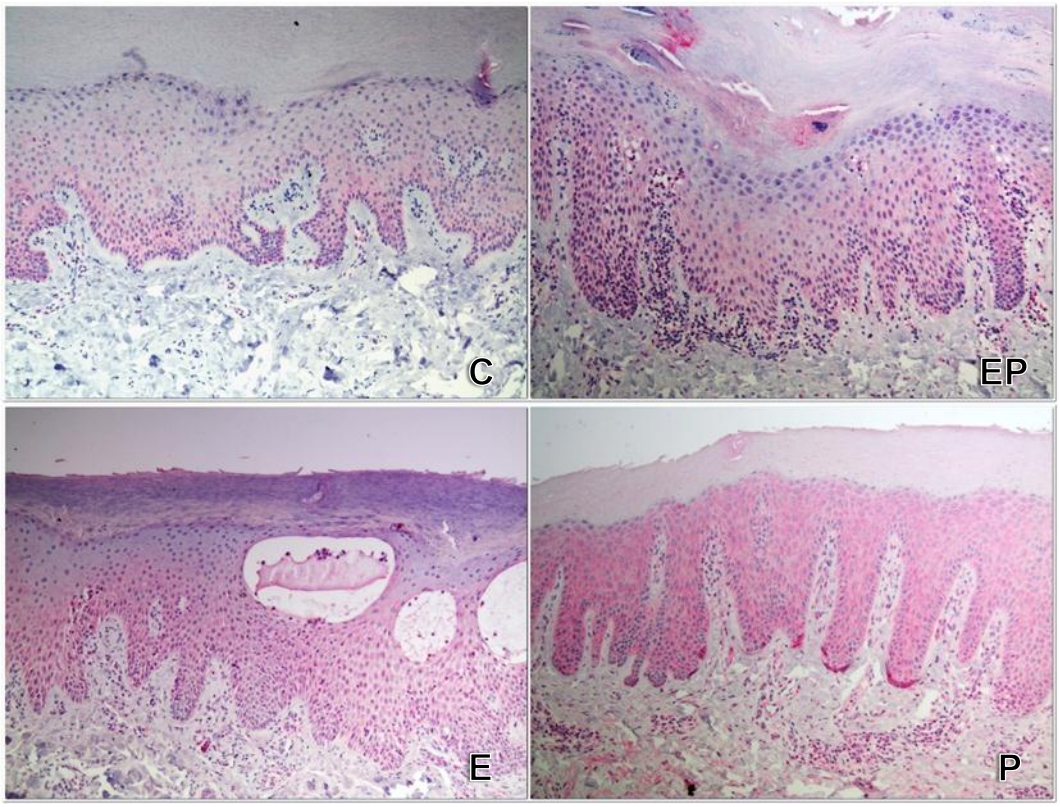

Figure 19. CD26 in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.4 Toll-like Receptor 4 (TLR4)

TLR4 staining shows positivity in stratum basale of all stained samples including healthy skin controls. Psoriasis turned out to have a weaker staining of basal keratinocytes than "eczema in psoriatico" ($p \leq 0.01$), allergic contact dermatitis ($p \leq 0.1$) and health controls.
Evaluation of suprabasal layers of epidermis did not show and significant differences between "eczema in psoriatico", contact dermatitis and psoriasis. Health controls turned out to have a weaker TLR4 expression than all examined inflammatory diseases ($p \leq 0.05$).
TLR4 expression in superficial layers of epidermis showed a slightly stronger reaction in psoriasis compared to allergic contact dermatitis ($p \leq 0.1$). There were no statistical differences between "eczema in psoriatico" and contact dermatitis. TLR4 staining in superficial layers in health controls was negative. All results are presented in Figure 20 and 21.

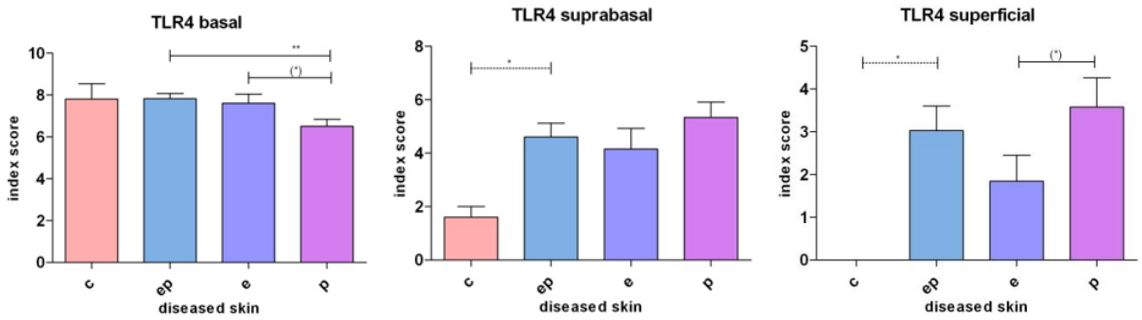

Figure 20. TLR4 in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy controls (c) accordingly in basal-, suprabasal- und superficial layers.

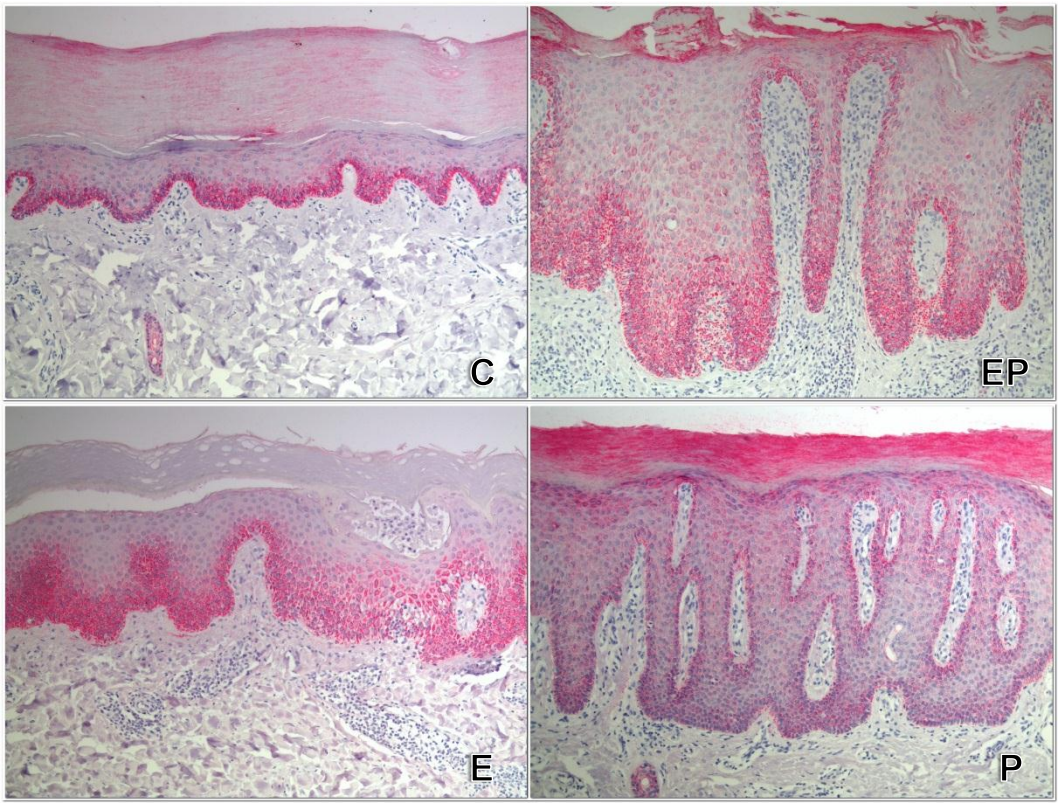

Figure 21. TLR4 in "eczema in psoriatico" (e), contact dermatitis (e), psoriasis (p) and in healthy controls (c).

5.1.5 Proliferation marker Ki67

The results of immunostaining with Ki67 are shown in Figure 22, 23 and 24. Proliferation rate was highest in psoriasis with a mean number of 144 Ki67 positive keratinocytes, moderate in "eczema in psoriatico" and in allergic contact dermatitis, (accordingly 99 and 81 positive cells) and low in healthy skin samples with a mean value of 48 positive cells. The major number of proliferating cells was distributed in stratum basale or directly suprabasal with a mean value of 97, 59, 43, and 37 accordingly in psoriasis, "eczema in psoriatico", allergic contact dermatitis and healthy skin samples. Statistical analysis using the Man-Whitney U test showed highly significant differences between psoriasis and contact dermatitis ($p \leq 0.01$), significant alterations between psoriasis and "eczema in psoriatico" ($p \leq 0.05$) and tendency ($p \leq 0.1$) between "eczema in psoriatico" and allergic contact dermatitis referring to Ki67 positive keratinocytes in the whole epidermis. These differences were more visible in stratum basale and directly suprabasal with highest significance ($p \leq 0.001$) between psoriasis and contact dermatitis and significance ($p \leq 0.05$) between psoriasis and "eczema in psoriatico" and between "eczema in psoriatico" and contact dermatitis. There were no statistical differences in the mean number of proliferating cells between psoriasis, "eczema in psoriatico" and contact dermatitis in upper stratum spinosum, stratum granulosum.

Evaluation of Ki67 in slides coming from patients without elevated IgE in serum showed some alterations as presented in Figure 23. Patients with "eczema in psoriatico" with IgE within normal range showed a higher number of Ki67 positive cells than corresponding patients with "eczema in psoriatico" and elevated IgE. Consequently, there were no statistical differences between psoriasis and "eczema in psoriatico" in the whole epidermis and in basal layers. Both, psoriasis and "eczema in psoriatico" turned out to have the highest number of Ki67 positive cells compared to lower number found in contact dermatitis ($p \leq 0.05$) and in healthy skin ($p \leq 0.05$).

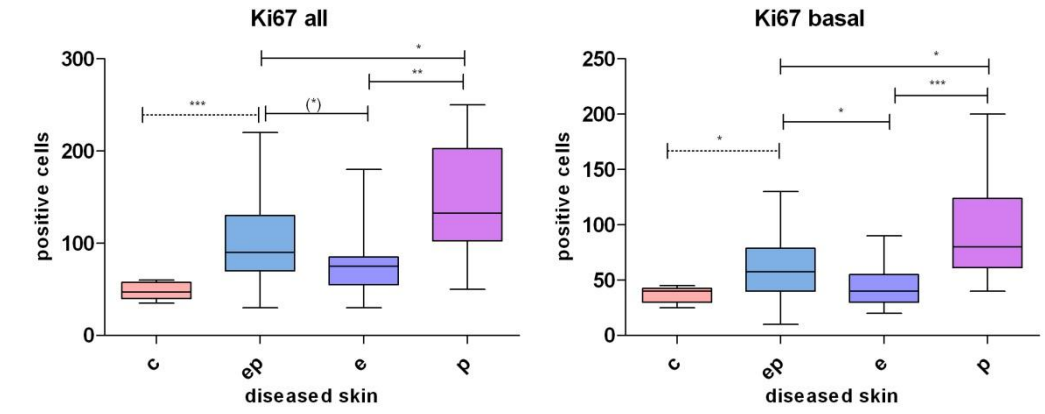

Figure 22. Ki67 positive cells in „eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

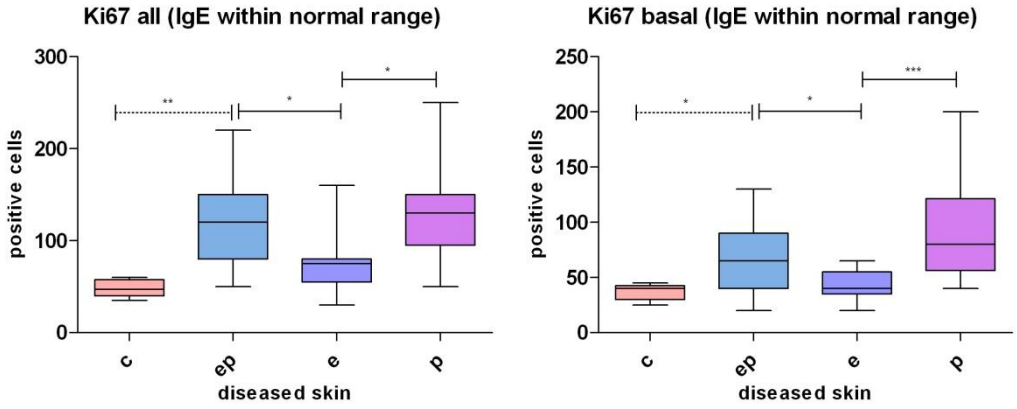

Figure 23. Ki67 positive cells in patients with IgE within normal range with "eczema in psoriatico"(ep),contact dermatitis (e), psoriasis (p) and in healthy skin (c).

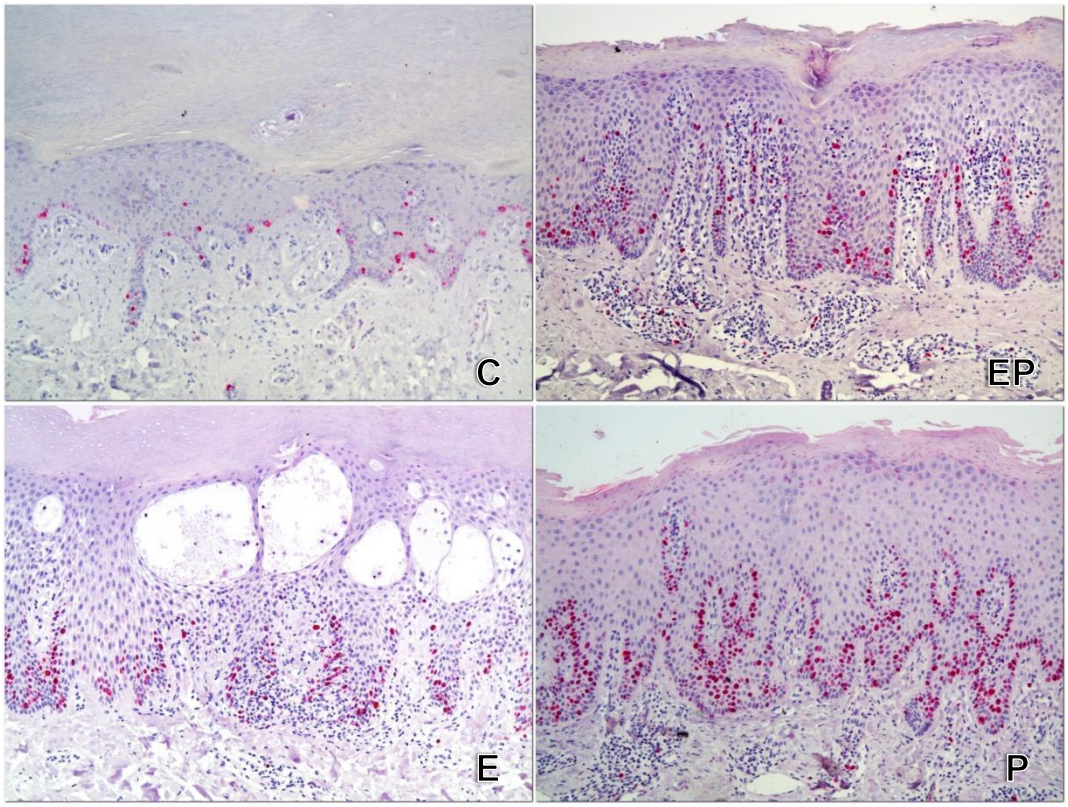

Figure 24. Ki67 positive cells in „eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.6 Langerhans cells (CD1a)

Dendritic cells were distributed throughout the epidermis and throughout the dermis in the inflammatory infiltrate. In all evaluated tissue samples, CD1a staining was stronger in epidermis than in dermis. In both epidermis and dermis, the highest number of positive cells was found in allergic contact dermatitis, followed accordingly by "eczema in psoriatico", psoriasis and healthy skin (Figure 25, 26 and 27).

Semi-quantitative analysis showed a statistical increase in the number of positive cells in epidermis in group of allergic contact dermatitis and "eczema in psoriatico" when compared

with the group of psoriasis (p≤0.01) and healthy skin samples (p≤0.001) (Figure 25). Less statistical differences were observed in the dermis with the highest number of positive CD1a in allergic contact dermatitis and "eczema in psoriatico" compared to psoriasis (accordingly p≤0.05 and p≤ 0.1).

The same evaluation performed in patients without elevated IgE in serum showed some changes, as presented in Figure 26. Also in those cases, contact dermatitis turned out to have the highest number of positive cells compared to patients with "eczema in psoriatico" (p≤0.05) and psoriasis (p≤0.01), both without elevated IgE in serum. Patients with "eczema in psoriatico" and IgE within normal range, have less CD1a positive cells compared to patients with "eczema in psoriatico" and elevated IgE and consequently, no statistical differences with psoriasis.

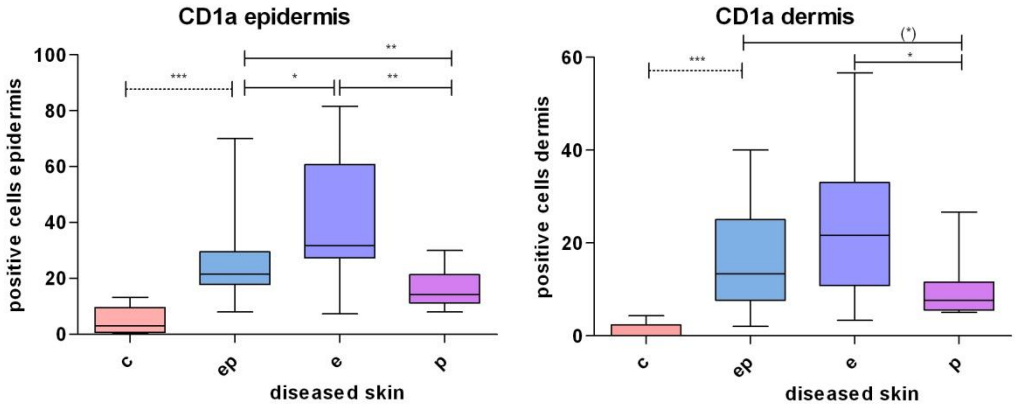

Figure 25. CD1a in "eczema in psoriatico", contact dermatitis (e), psoriasis (p) and in healthy skin (c).

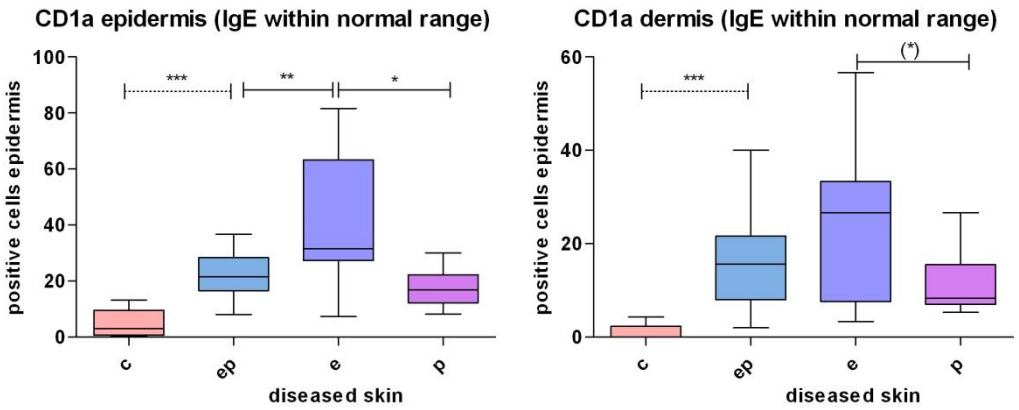

Figure 26. CD1a in patients with IgE within normal range with "eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

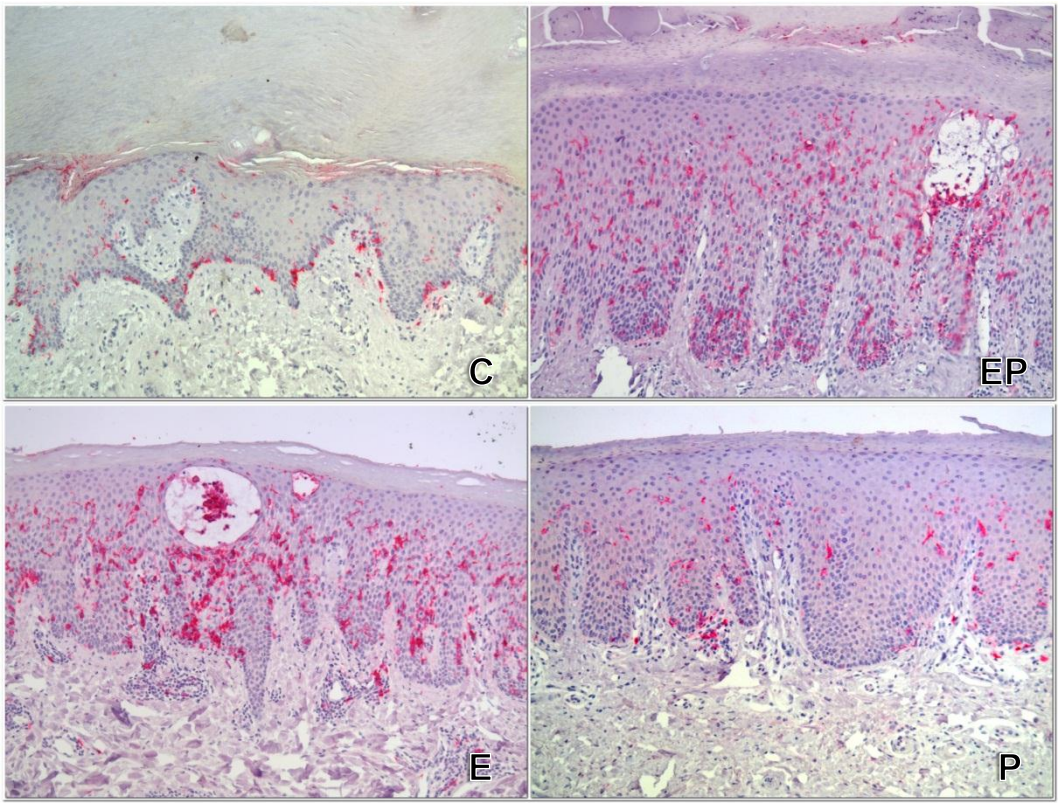

Figure 27. CD1a in „eczema in psoriatico"(ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.7 Major histocompatibility complex I (MHC I)

The positive staining (membrane-like pattern with pericellular delineation) was observed in basal- and suprabasal epidermis layers. All examined slides showed positive staining in stratum basale and negative staining in superficial layers. Significant differences were observed only in the suprabasal layer: contact dermatitis and "eczema in psoriatico" showed MHC I overexpression, compared to psoriasis ($p \leq 0.001$) and to samples of healthy skin ($p \leq 0.001$). There were no statistical significant differences in the number of MHC I-positive cells in dermal infiltrate between psoriasis, contact dermatitis and "eczema in psoriatico". All results are illustrated in Figure 28 and 29.

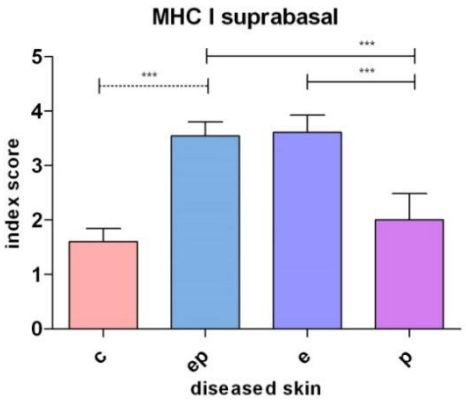

Figure 28. MHC I in suprabasal layers in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p), and in healthy skin (c).

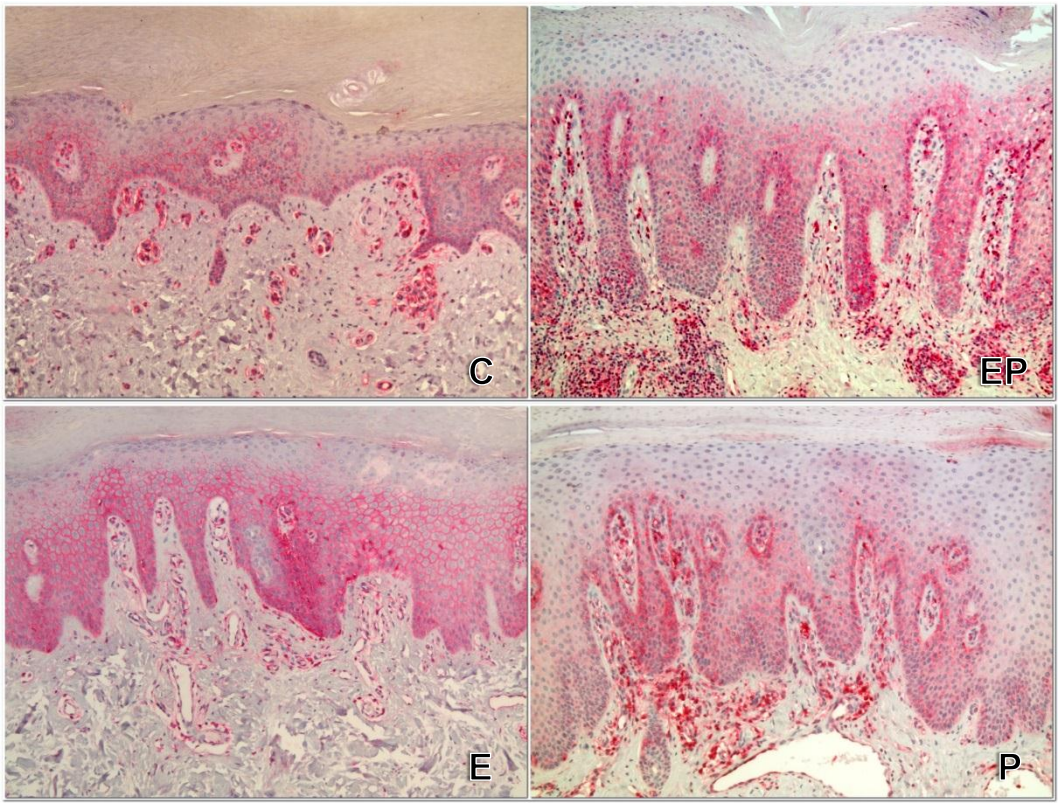

Figure 29. MHC I in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.8 Major histocompatibility complex II (MHC II)

MHC II positive cells were observed in epidermis and in dermis of all examined inflammatory diseases (ep, e, p).

MHC II staining shows an increased number of positive cells in epidermis with Langerhans cells and lymphocytes morphology in contact dermatitis and in "eczema in psoriatico," compared to psoriasis (accordingly $p \leq 0.01$ and $p \leq 0.001$) and healthy controls ($p \leq 0.001$) (see Figure 30 and 31). MHC class II molecules were rarely expressed by keratinocytes.

An elevated number of MHC II positive cells in dermis was observed in all inflammatory diseases, compared to healthy controls ($p \leq 0.001$). There were no statistical differences in the number of MHC II-positive cells in dermal infiltrate between psoriasis, contact dermatitis and "eczema in psoriatico".

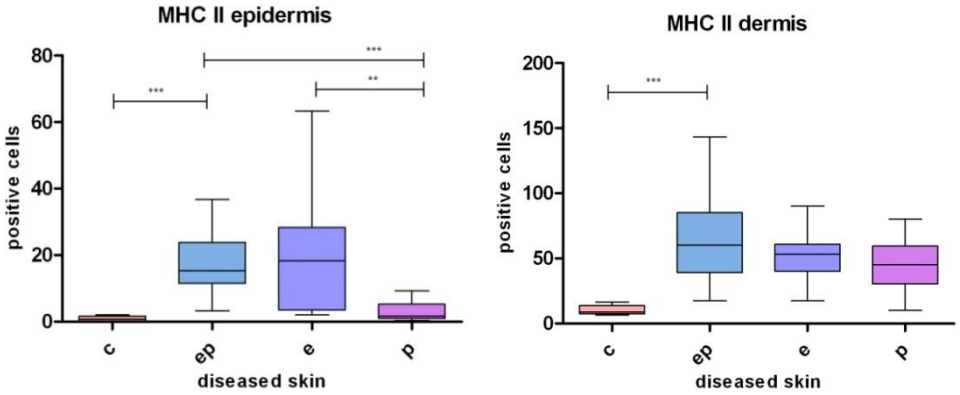

Figure 30. MHC II in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

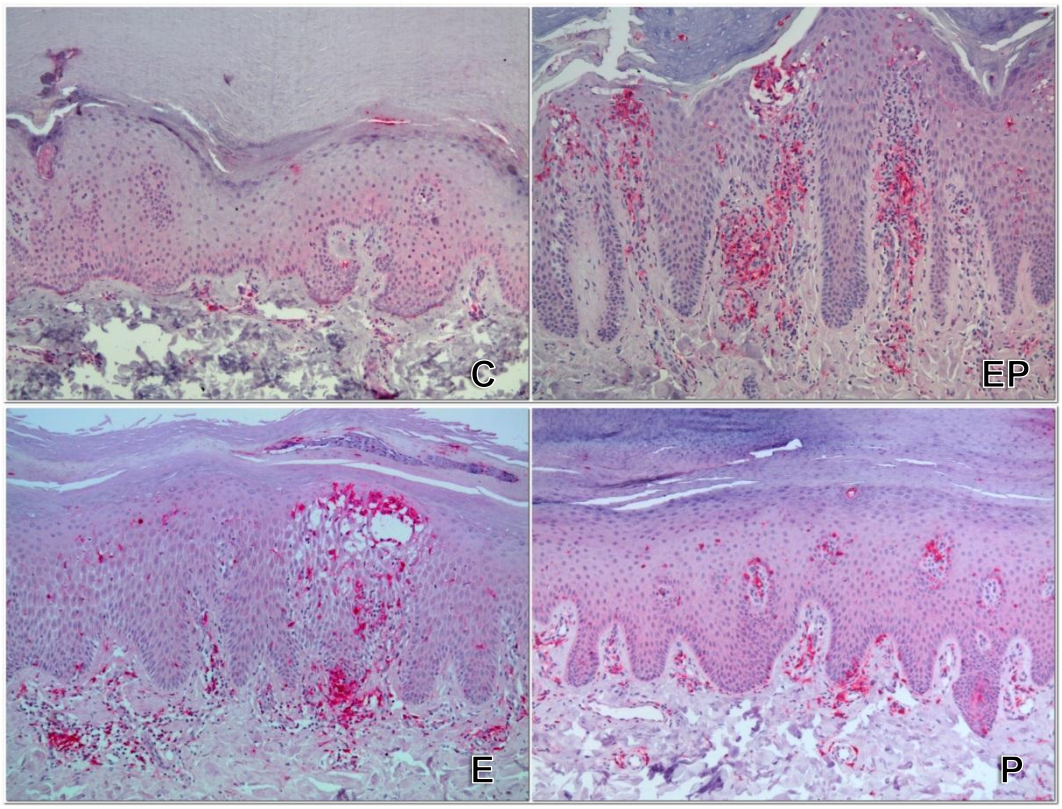

Figure 31. MHC II in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.9 T-cell subsets: CD4+ and CD8+

The number of CD4+ and CD8+ T cells in both epidermal and dermal compartments; as well CD4+/CD8+ ratios are presented accordingly in Table 8 and Figure 32.

Illness	*Contact dermatitis e n=13*	*Psoriasis p n=12*	*Eczema in psoriatico ep n=33*	*Healthy skin c n=5*
CD4/CD8 ratio epidermis:	1.68	1.31	0.92	0.75
CD4/CD8 ratio dermis:	1.92	1.31	1.62	1.32

Table 8. CD4/CD8 ratio in contact dermatitis (e), psoriasis (p), "eczema in psoriatico"(ep) and in healthy skin (c).

There was an increased number of both CD4+ and CD8+ T-cell subsets in epidermal compartment in allergic contact dermatitis and in "eczema in psoriatico," in comparison with psoriasis ($p \leq 0.001$) and healthy skin ($p \leq 0.001$). Regarding CD4/CD8 ratio, "eczema in psoriatico" showed, in contrary to allergic contact dermatitis and psoriasis, the dominance of epidermal CD8+ T cells over epidermal CD4+ T cells. Dominance of CD8+ T cells over CD4+ T cells was also observed in epidermis of healthy skin samples.

CD4/CD8 ratio in dermis was highest in contact dermatitis (1.92), moderate in "eczema in psoriatico" (1.62) and lower in psoriasis (1.31) and in healthy skin (1.32). Regarding the number of CD4+ T cells in dermis, there were no statistical differences between eczema, "eczema in psoriatico" and psoriasis. All three diseases (ep, e, p) showed an up-regulated number of CD4+ T cells in dermis, compared with healthy skin ($p \leq 0.001$).

Surprisingly, in "eczema in psoriatico", there was an highly increased number of dermal CD8+ T cells, compared not only with healthy skin ($p \leq 0.001$), but also with allergic contact dermatitis ($p \leq 0.01$) and psoriasis ($p \leq 0.001$). This phenomenon is illustrated in Figure 33.

Evaluation of T-cell subsets in patients without elevated IgE did not show any significant differences regarding CD4+ T cells in epidermis and dermis, as well as epidermal CD8+ T cells in all examined diseases. Patients with "eczema in psoriatico" without increased IgE in serum also showed an elevated number of dermal CD8+ T cells compared to contact dermatitis and psoriasis. These differences were statistically less prominent and accounted in both cases: $p \leq 0.05$.

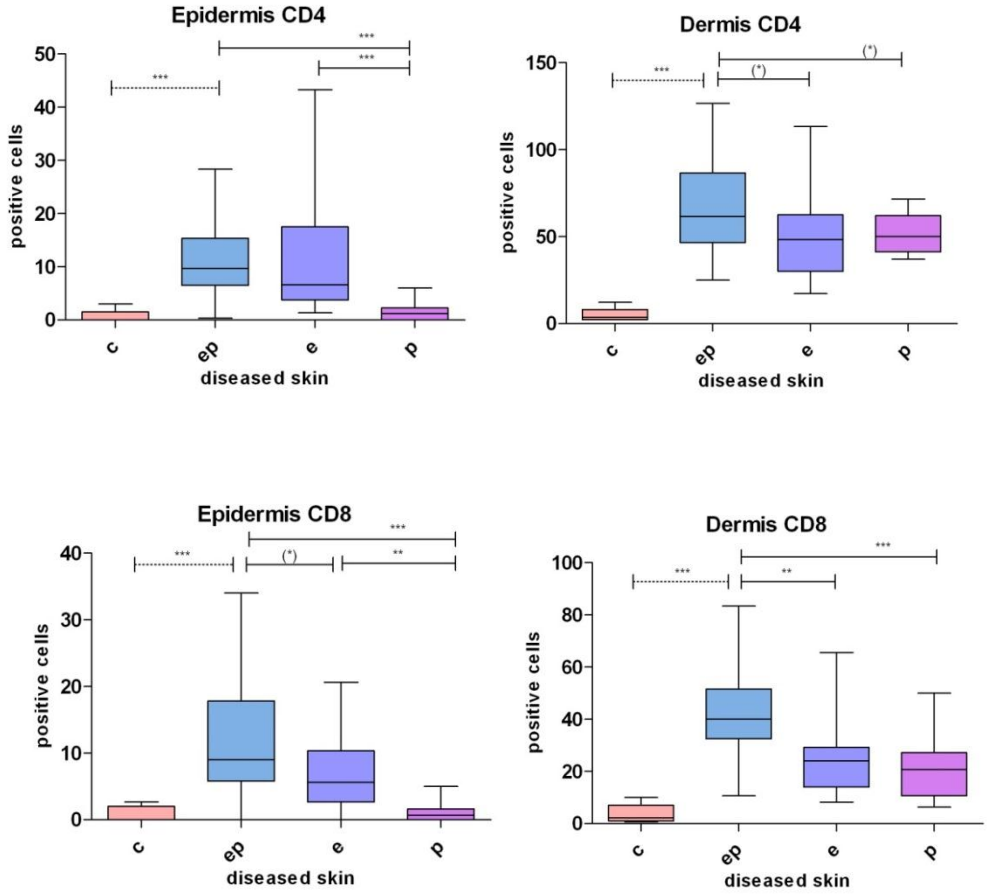

Figure 32. T-cell subsets in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in helathy skin (c).

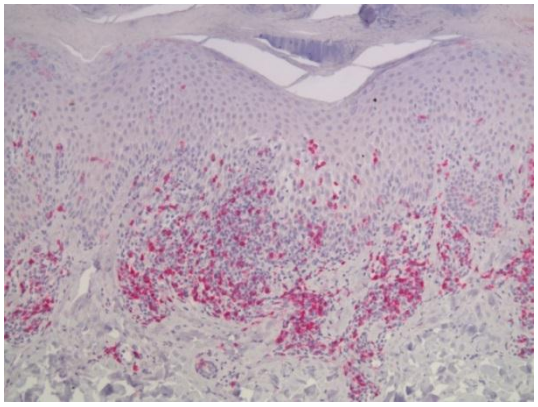

Figure 33. Overexpression of CD8+ T cells in dermis of "eczema in psoriatico".

5.1.10 Interleukin 8 (IL-8)

IL-8 was positively stained in neutrophils, accumulated in stratum corneum and subcorneal (Figure 34). At the same time, IL-8 showed a distinct, intercellular, desmosome-like pattern in basal and suprabasal keratinocytes and in inflammatory infiltrate in dermis (Figure 35). In single cases, especially in "in the field of" of acriosyringium, there was intracellular keratinocyte reactivity.

Due to accumulation of IL 8-positive neutrophils in parakeratosis, IL-8 staining in stratum

corneum was highest in psoriasis, moderate in “eczema in psoriatico” and lowest in allergic contact dermatitis. Statistical evaluation was as followed p≤0.01 between psoriasis and contact dermatitis and p≤0.05 between psoriasis and “eczema in psoriatico” and between “eczema in psoriatico” and contact dermatitis (Figure 34).

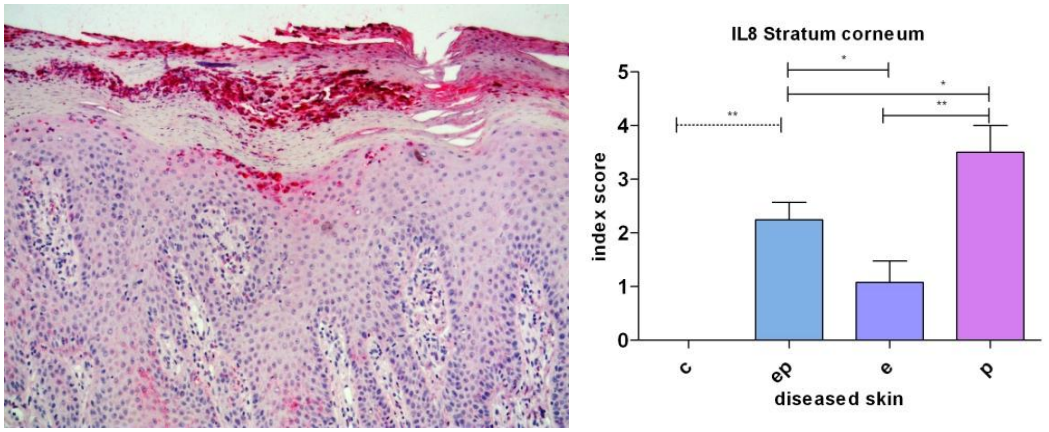

Figure 34. IL-8 positive neutrophils subcorneal und in stratum corneum in psoriasis.

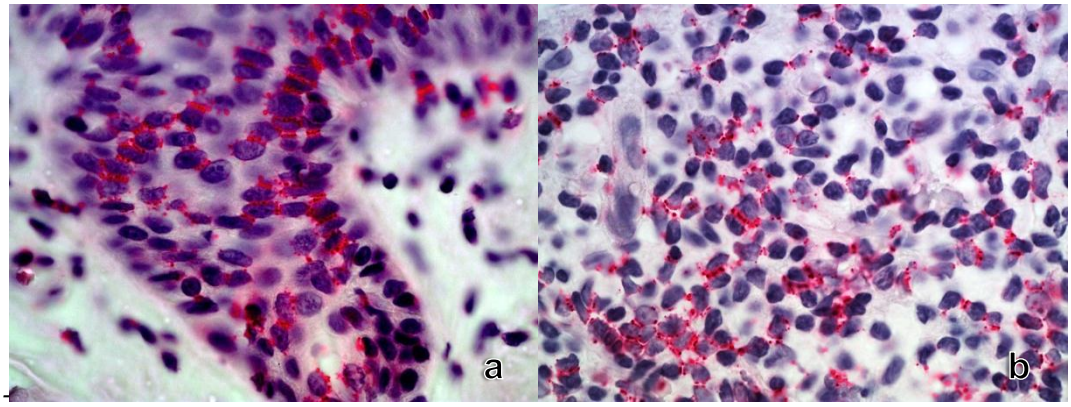

Figure 35. a: Desmosome-like pattern in basal- and suprabasal layers in contact dermatitis (e); b: desmosome-like pattern in dermal infiltrate in contact dermatitis (e).

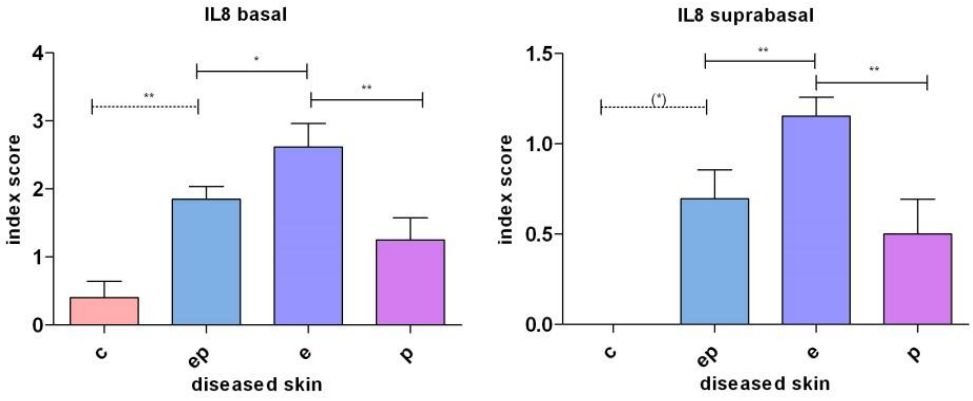

Figure 36. IL-8 desmosome-like staining in contact dermatitis (e), psoriasis (p), "eczema in psoriatico" (ep) and in healthy skin (c).

As presented in Figure 35 and 36, the IL-8 desmosome-like staining was most prominent in the basal layer of epidermis. We observed a statistical significant overexpression of IL-8 in

allergic contact dermatitis when compared with psoriasis (p≤0.01) and with "eczema in psoriatico" in both basal- and suprabasal- layers (accordingly p≤0.05 and p≤0.01). There were no statistical significant differences between contact dermatitis, psoriasis and "eczema in psoriatico" in superficial part of epidermis. No statistical differences were seen in dermal infiltrate.

5.1.11 Interleukin 17 (IL-17)

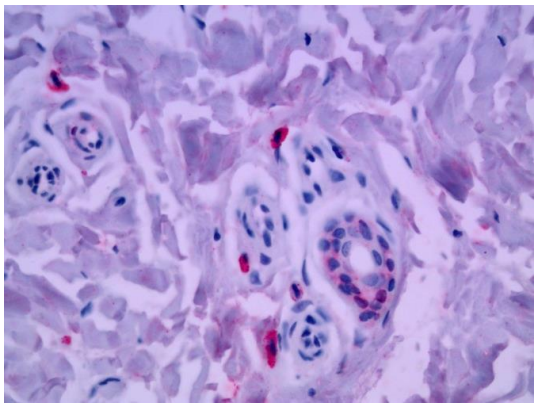

Figure 37. IL-17 positive cells with morphology of mast cells.

IL-17 positive cells were found in the upper and lower dermis. Analysis of skin samples by immunochemistry with IL-17 demonstrated IL- 17 in cells with neutrophil-, dendritic cell-, and especially, mast cell morphology (Figure 37). Healthy skin controls showed statistically decreased numbers of IL-17 positive cells compared with "eczema in psoriatico" in both upper- and lower dermis (p≤0.01). There were no statistical differences in the number of positive cells between psoriasis and "eczema in psoriatico" (both increased number). Semi-quantitative analysis of positive cells in the lower dermis showed a high significant increase (p≤0.01) in psoriasis group when compared with contact dermatitis and a tendency (p≤0.1) comparing "eczema in psoriatico" with contact dermatitis (Figure 38). These differences were less apparent in upper dermis- a statistically significant increase of IL-17 positive cells (p≤0.05) was observed only in case of psoriasis compared with contact dermatitis.

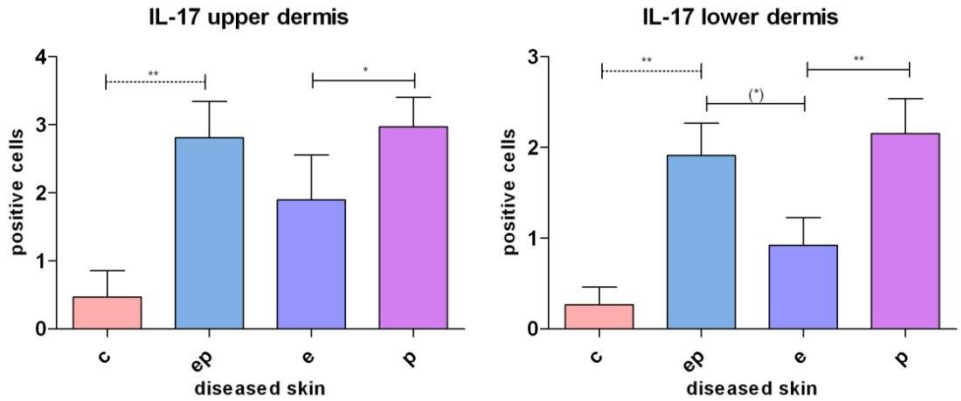

Figure 38. IL-17 in upper- and lower dermis of "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and in healthy skin (c).

5.1.12 Interleukin 23 (IL-23)

IL-23 positive cells were found mostly in papillary dermis (intravasal) and in Munro microabscesses. Most of the IL-23 positive cells had neutrophils' morphology (Figure 39).

There was an increased number of IL-23 positive cells in psoriasis and in "eczema in psoriatico," compared to allergic contact dermatitis (accordingly p≤0.01 and p≤0.5). No statistical differences in the number of Il-23 positive cells were observed between psoriasis and "eczema in psoriatico". The results are presented in Figure 40. IL-23 positive cells were not observed in healthy skin.

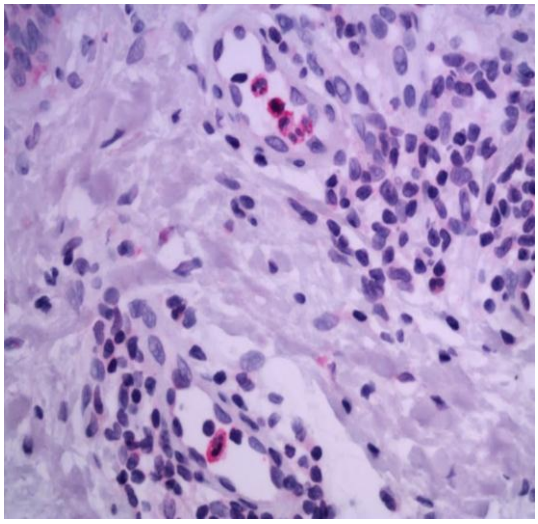

Figure 39. IL-23 positive cells with neutrophils morphology.

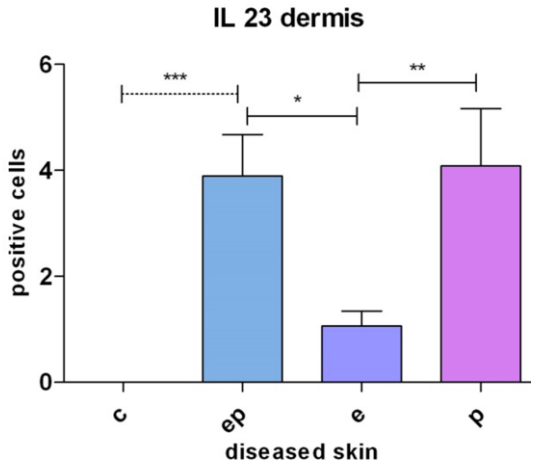

Figure 40. IL-23 positive cells in "eczema in psoriatico" (ep), contact dermatitiis (e) psoriasis (p) and in healthy skin (c).

5.1.13 Interleukin 31 (IL-31)

IL-31 positive cells were distributed mainly throughout the upper dermis. IL-31 positive cells mostly had morphology of dendritic- and mast cells (Figure 41). Semi-quantitative analysis showed a statistical increase in the number of positive cells in group of "eczema in psoriatico" and contact dermatitis when compared with the group of psoriasis (accordingly p≤0.05 and p≤0.1) and healthy skin (p≤ 0.001) (Figure 42).

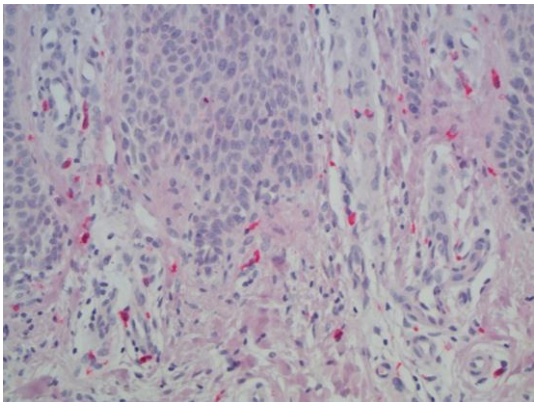

Figure 41. IL-31 positive cells in dermis of "eczema in psoriatico".

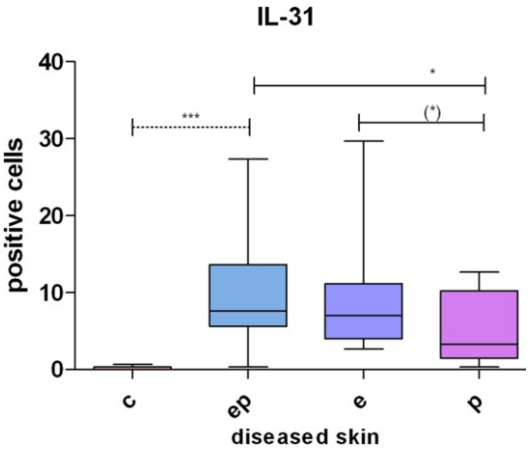

Figure 42. IL-31 positive cells in "eczema in psoriatico" (ep), contact dermatitis (e), psoriasis (p) and healthy skin (c).

The same evaluation performed on slides coming from patients without elevated IgE levels

in serum did not show any statistical differences in the number of IL-31 positive cells between "eczema in psoriatico", contact dermatitis and psoriasis.

5.2 Discussion immunohistology

5.2.1 Filaggrin

Filament aggregating protein (filaggrin) is the main component of keratohyalin granules located in stratum granulosum. Filaggrin shows a strong reactivity in healthy skin, encompassing 3-4 layers of stratum granulosum. A reduced filaggrin expression can be a result of alterations in epidermal differentiation or of filaggrin-loss-of-function mutations. Filaggrin carrier mutations status affects 8 to 10% of adults from the whole population [57,58] and up to 30-50% of patients with atopic dermatitis, particularly with severe course [59]. Its deficiency leads to impaired skin barrier with an elevated transepidermal antigen penetration and an elevated water loss [60]. It is known that disruption of the skin barrier can lead to skin dryness [61] and to the development of ichthyosis vulgaris [62], atopic dermatits [57] or contact dermatitis of allergic or irritant type [63]. It was observed [64,65] that patients with filaggrin-loss-of-function mutations and no history of atopic dermatitis have more often dorsal hyperkeratosis, palmar hyperlinearity and intermittent skin fissures, especially during the winter. Dorsal skin changes (and sparse involvement of palms) in the "filaggrin hand eczema" was due to higher environmental exposure in that localisation.

A reduced filaggrin expression in psoriasis has been already described, [36] and was discussed to reflect an altered epidermal differentiation (loss of stratum granulosum) and not genetic background with loss-of-function variants of the filaggrin gene. Filaggrin deficiency in psoriasis was also confirmed by Kim et al. [66]. It was suggested, that its origin is acquired and connected with TNF-α modulation. Treatment with anti-TNFα was found increased expression of filaggrin and loricrin in psoriatic lesions [67]. Profilaggrin and filaggrin reactivity in keratinocytes was found to be down-regulated by IL-22 [68]. Restoration of filaggrin positive cells was also observed under the therapy with calcipotriol [69].

Our study, "eczema in psoriatico" showed reduced filaggrin expression compared not only to contact dermatitis ($p<0.001$), but also to psoriasis ($p<0.05$). These results reflect alterations in epidermal differentiation with consecutive loss or thinning of stratum granulosum. Similar changes, but less prominent ones were observed in case of psoriasis. It can be speculated, that other factors such as type IV-sensitisation, atopy and irritants influence additional filaggrin production and its distribution in "eczema in psoriatico".

On the other hand, examined slides with contact dermatitis had mostly "normal" and "linear" (=slightly reduced) filaggrin patterns, which could be explained by our inclusion criteria. Irritant palmoplantar eczema, as well as isolated atopic hand- and foot dermatitis cases were excluded from this study. Furthermore, the examined patients in particular, had a

palmoplantar manifestation - not as in case "filaggrin hand eczema" the involvement of dorsal sides of hands.

5.2.2 Cytokeratines 16 and 17 (CK16, CK17)

Cytokeratines are the basic structural components of keratinocytes. Basal keratinocytes normally express CK5 and CK14 and suprabasal keratinocytes: CK1 and CK10 [70,71].

CK16 reactivity is observed in the hyperproliferating epidermis of psoriasis, but not in healthy skin [70]. CK17 is not detected in normal human epidermis; and it is restricted to moyepithelial cells of the sweat glands and the deep outer root sheath [72]. Expression of CK17 in psoriatic epidermis is similar to that of CK16. Correspondingly, both CK16 and CK17 are postulated as sensitive markers of keratinocyte hyperproliferation in psoriasis, [70] and are useful in the evaluation of anti-psoriatic therapies. Reactivity of CK16 and CK17 in epidermal psoriasis was found to be reduced after the local treatment with anthralin and vitamin D3-analogue [72]. Changes in distribution of CK16 in psoriasis with normalisation in basal- and suprabasal layers were observed under the therapy with cyclosporin [71]. Diminution of CK17 expression was observed also under the treatment with adalimumab [67]. Acitretin decreased, whereas hydrocortisone increased CK17 reactivity in a HaCaT keratinocyte model [73].

There are only a few studies examining the expression of CK16 and/or CK17 in contact dermatitis. Willis et al. demonstrated high level expression of CK16 and only moderate expression of CK17 during the course of irritant contact dermatitis induced by sodium lauryl sulfate [74]. Le et al. observed marked increased epidermal reactivity of CK16 in both allergic and irritant contact dermatitis [75] and in other studies in 5 of 11 patients with chronic irritant contact dermatitis [76].

CK16- and CK17- expression turned out to be positive in psoriatic epidermis and negative in samples of healthy skin, as described by other authors [70,72]. In psoriasis, both stainings were positive in superficial- and suprabasal layers (whole stratum suprabasale in case of CK16 and upper suprabsasal layers in case of CK17). Similarly to other studies [74-76], CK16 reactivity in contact dermatitis was also elevated, with positivity of suprabasal- and superficial layers. In comparison, CK17 showed only a slight increased expression in palmoplantar contact dermatitis compared with healthy skin and decreased expression compared with psoriasis ($p< 0.05$). This is why CK17, but not CK16 appears to be useful in differentiation of epidermal hyperproliferation between palmoplantar psoriasis and allergic contact dermatitis.

Reactivity of CK16 and CK17 in "eczema in psoriatico" was increased and corresponded to that found in psoriasis. These results showed that "eczema in psoriatico" had the same alterations in epidermal hyperproliferation as psoriasis.

5.2.3 Dipeptidyl peptidase IV (CD26)

CD26 (Dipeptidyl peptidase IV = DP IV) is a membran glycoprotein with proteolytic properties. Inhibition of ectopeptidases like CD26 was found to influence different biological processes such as growth, apoptosis, differentiation and angiogenesis [77-79]. Inhibition of CD26 affects growth and functions of peripheral T lymphocytes [80]. In human skin, CD26 is expressed on keratinocytes [81], sebocytes [82] and fibroblasts [83,84]. It was proved, that inhibitors of DP IV suppress keratinocyte proliferation in vitro [81] and may restore keratinocyte differentiation in vivo [85].

CD26 is known to be up-regulated in various inflammatory diseases like psoriasis and spongiotic diseases [86].

Van Lingen et al. [87] demonstrated an epidermal overexpression of CD26 in psoriatic plaques, compared to uninvolved psoriatic skin and the healthy volunteers skin. Savoia et al. [88] observed normalised (reduced) reactivity of CD26 in psoriasis after treatment with calcipotriol. Psoriasis patients were found to have decreased CD26 expression of peripheral blood CD8+ T-cell subsets [89,90]. It was speculated, that this reduction may represent redistribution of activated T cells into the dermal compartment [90].

Increased CD26 reactivity in epidermis (with punctum maximum in stratum basale) was also observed in patients with atopic dermatitis and allergic contact dermatitis [91]. Similar results were demonstrated in both rat models of contact hypersensitivity [91].

Our findings regarding psoriasis and contact dermatitis showed, in accordance to previous studies, an enhanced expression of epidermal CD26 staining in both diseases. To our knowledge, there are no studies comparing the reactivity of CD26 between psoriasis and chronic contact dermatitis. In our evaluation, psoriasis turned out to have stronger reactivity than contact dermatitis, especially in superficial layers ($p \leq 0.1$). "Eczema in psoriatico" showed a similar pattern to contact dermatitis. We demonstrated the statistical differences in CD26 staining between psoriasis and "eczema in psoriatico", with stronger expression in the case of psoriasis in suprabasal- und superficial layers (accordingly $p \leq 0.05$ and $p \leq 0.01$).

5.2.4 Toll-like Receptor 4 (TLR4)

Toll like receptors (TLRs) are a family of cellular surface protein receptors, which recognise pathogen-associated molecular patterns. TLRs are part of an innate system and initiate antimicrobial responses in various cells [92]. There are at least 10 functional TLRs, which have been identified in humans. TLR4 acts as a receptor of lipopolysaccharide (LPS) of gram-negative bacteria inducing production of different cytokines and chemokines.

It was proven, that human keratinocytes express TLR2 and TLR4 and play an important role as component of innate immunity [93].

As microbial pathogens are known to aggravate psoriasis, TLRs were suggested to play a role in patomechanism of psoriasis. Resistance of psoriatic plaques to superinfection by

Staphylococcus aureus was also explained through increased levels of antimicrobial peptides found in psoriatic scales [94]. Expression of TLR and its role in psoriasis was investigated by different authors. Baker et al. observed an increased reactivity of TLR1, TLR2 and reduced reactivity of TLR5 compared psoriasis with normal skin[95]. TLR4 was found to be expressed by epidermal and dermal DCs and mid-epidermal KCs [96]. Due to an increased reactivity of TLR4 in psoriasis guttata, compared with psoriasis of plaque type, TLR4 was shown to play a role its pathogenesis [97]. TLR 4 was found to be a potent agonist of monomethylfumarate [98].

TLR2 and TLR4 were proven to play a pivotal role in experimental model of allergic contact dermatitis [99]. Two different mechanisms were suggested. In IL-12-independent one, mice lacking both TLR2 and TLR4 failed to develop contact hypersensitivity. In IL-12-dependent one, failing response to IL-12 and the absence of single TLR2 or TLR4 prevents the development of contact dermatitis. TLR4 is also known to play a crucial role in the development of contact allergy to nickel [100]. Schmidt et al have identified, that beside a hapten-specific T cell response, nickel can directly activate innate immune system via TLR4.

In our observation, TLR4 showed an accentuation of stratum basale in healthy skin, allergic contact dermatitis and in "eczema in psoriatico". Psoriasis turned out to have a weaker staining in basal layers than all other inflammatory diseases ($p \leq 0.05$) and also than healthy skin. On the other hand TLR4 staining in psoriasis showed reactivity in whole epidermis with tendency to up-regulation in superficial layers, when compared to ACD ($p \leq 0.1$). The TLR4 pattern in "eczema in psoriatico" was similar to that - found in allergic contact dermatitis.

5.2.5 Proliferation marker Ki67

Ki67 is a proliferation marker, detecting a human nuclear antigen presented in proliferating cells [101]. Normal skin renewal is assisted by stem-like cells, of which only a small percentage can be triggered to proliferate [102]. Hyperproliferation of epidermal keratinocytes is one of the main characteristic features of psoriatic plaque. Expression of Ki67 was found to correlate with the psoriasis severity and was reduced under successful treatment, with for example, retinoids, methotrexate or cyclosporine [103-106].

There are only a few studies [107,108] examining the proliferation rate in contact dermatitis and to our knowledge, only single comparisons between psoriasis and eczema.

Our study showed, that Ki67-positive cells were more abundant in psoriasis than in contact dermatitis and healthy skin (in the whole epidermis, respectively $p \leq 0.01$ and $p \leq 0.001$). "Eczema in psoriatico" turned out to have moderately increased number of proliferating cells, lower than psoriasis ($p \leq 0.05$) and slightly higher than contact dermatitis ($p \leq 0.1$ in the whole epidermis and $p \leq 0.05$ in the basal layer).

Interestingly the same evaluation in patients without elevated IgE in serum revealed enhanced number of Ki67 positive cells compared to patients with increased IgE. Consequently,

patients with “eczema in psoriatico”, who have a normal range of IgE showed the same proliferation activity as patients with psoriasis.

It can be speculated, that cellular turnover taking place in “eczema in psoriatico” can be decreased (in comparison to psoriasis) due to contemporary processes, characteristic for contact sensitisation and atopy.

5.2.6 Langerhans cells (CD1a)

Cutaneous dendritic cells (DCs) can be divided in epidermal DCs (Langerhans cells, LCs) and dermal DCs (myeloid DCs and plasmacytoid DCs).

Langerhans cells are antigen-presenting cells, representing 2-5% of the epidermal cell population [109]. These play a crucial role in the development of allergic contact dermatitis. LCs are located fundamentally in suprabasal cell layers, where are bond to keratinocytes by E-cadherins [110]. After antigen uptake, activated Langerhans cells move into dermis, enter lymphatic vessels, travel to the lymph nodes and present the antigen via MHC molecules to T lymphocytes. The role of LCs in psoriasis is not completely assessed. It was shown, that TLR-2 induced LCs can prime Th17 cells via IL-23, IL-1 β and TGF-β [111]. However, there are conflicting results regarding the number or density of LC in psoriasis. It is probably connected with different LC numbers in the different stages or localisations [112]. Komine et al. [112] demonstrated that the number of LC was highest in the perilesional skin compared to lesional- and nonlesional psoriatic skin. Knowing that psoriatic plaque develops eccentrically, it was suggested that LCs play an important role in the early plaque formation. Decreased densities of LCs in psoriatic lesions were also found by Gordon KB et al. [113]. Restoration of epidermal DCs was observed by under the treatment with reinoids [114], psoralen plus ultraviolet (UV) A [115] , UVB [116] or ciclosporin [117] or adalimumab [113].

Cumberbatch M et al. [118] proved an impaired Langerhans cell migration in psoriasis compared to healthy skin of volunteers. These findings were confirmed also by Soyland et al [119]. It was observed that the count of CD1a positive cells in epidermis was reduced in lesional psoriatic skin compared to non-lesional psoriatic skin (in dermis, there were no significant differences). Sun exposure leads to further reduction in LC number in epidermis, especially in non lesional skin. Only a slight reduction of LC numbers in lesional psoriatic epidermis suggested, according to authors, an impaired migratory function [119].

Dermal dendritic cells (dDCs) are also found to be of great importance in the pathogenesis of many inflammatory diseases. Several studies examined dDCs in the pathogenesis of psoriasis.

Myeloid DCs expressing CD11c were found to be increased in number 30-fold compared psoriasis to healthy skin [120]. Myeloid DCs are important in the psoriasis' pathogenesis through its stimulation of Th1/Th17 T lymphocytes and production of numerous cytokines and chemokines, such as TNF-α or INF-α. It was observed, that lesional psoriatic skin, but

not skin from healthy donors contained DCs expressing IL23p19, which are known to promote the development and activation of Th17 cells [121].

Antipsoriatic therapies such as PUVA or TNFα inhibitors were found to reduce the number of dermal dendritic cells [122]. Clinical improvement was observed under therapy with humanised antibody anti-CD11a efalizumab, which led to reduction of myeloid DCs (medicine withdrawn from the market because of risk of progressive multifocal leukoencephalopathy) [123].

Plasmacytoid DCs expressing CD123 produce INF-α during viral infections, which stimulates and regulates T lymphocytes and myeloid DCs [122]. INF-α produced by plasmocytoid DCs was found to play a role in the pathophysiology of psoriasis.

Dendritic cells play an important role in atopic dermatitis and their number correlates with the disease activity [124,125].

CD1a, an antibody directed against MHC molecules [126,127], is specific for LCs, but it can also be expressed on dermal dendritic cells [128].

In our study, we performed only CD1a immunostaining. Our results confirm that epidermal LCs are highly increased in allergic contact dermatitis compared to healthy skin. The number of epidermal LCs in psoriasis turned out to be slightly higher than in healthy controls and statistically lower ($p \leq 0.01$) than in case of allergic contact dermatitis. The low number of epidermal CD1a positive cells in psoriasis may depend on the localisation (in our case lesional skin samples) and on already described impaired migratory functions of LCs in psoriasis. "Eczema in psoriatico" showed more similarities with allergic contact dermatitis than with psoriasis. The count of epidermal LCs cells was lower than in allergic contact dermatitis ($p \leq 0.05$) and at the same time higher than in psoriasis ($p \leq 0.01$) and in healthy skin ($p \leq 0.001$). In the dermal compartment, the differences were less significant.

The same evaluation performed in patients without elevated IgE in serum, revealed "psoriasiform" pattern of "eczema in psoriatico". There were no statistical differences between "eczema in psoriatico" and psoriasis in the number of CD1a positive cells. Furthermore, chronic dermatitis turned out to have an elevated count of Langerhans cells, statistically higher than that of psoriasis ($p \leq 0.05$) and "eczema in psoriatico" ($p \leq 0.01$) without atopy.

It can be speculated, that further characterisation of infiltrating DCs with other markers could enable a better understanding of the pathomechanism of "eczema in psoriatico". Coexisting atopy (elevated IgE levels) turns out to influence the number of CD1a positive cells in "eczema in psoriatico".

5.2.7 Major histocompatibility complex I (MHC I)

MHC class I molecules are expressed at the surface of all nucleated cells and take part in presentation of endogenous peptide antigens to CD8+ cytotoxic T cells [31]. Expression of

MHC molecules is increased by cytokines production during both innate and adaptive immune responses.

The staining pattern of MHC I in psoriasis and in contact dermatitis has rarely been examined. Carlén et al. [129] observed variable expression levels of HLA-C (MHC class I heavy chain receptor) in epidermis between psoriasis and eczema. In psoriasis samples, there was a strong immunoreactivity of HLA-C in the basal cell layer and weak in suprabasal layers, whereas in contact dermatitis, a strong immunoreactivity in suprabasal layers was shown.

Our findings are partially in accordance with the results of Carlén et al. [129]. We did not observe any statistical differences in MHC I reactivity between contact dermatitis, psoriasis, "eczema in psoriatico" and healthy skin in basal layers. The evaluation of MHC I staining in suprabasal layer appeared to be useful in differentiation of palmoplantar psoriasis from palmoplantar allergic contact dermatitis (highest significance in MHC I up-regulation in contact dermatitis compared to psoriasis). "Eczema in psoriatico" showed a similar pattern to contact dermatitis with strong reactivity within basal- and suprabasal epidermis layers ($p \leq 0.001$ in suprabasal layers comparing "eczema in psoriatico" with psoriasis).

Enhanced expression of MHC I molecules in allergic contact dermatitis and "eczema in psoriatico" correlate with elevated number of Langerhans cells and CD8+ T cells in epidermis in both diseases. In case of psoriasis, weaker reactivity of MHC I corresponded to lower number of Langerhans cells and of epidermal CD8+ T cells, in comparison to allergic contact dermatitis and "eczema in psoriatico".

5.2.8 Major histocompatibility complex II (MHC II)

MHC class II molecules are expressed on the antigen-presenting cells and present exogenous antigenic peptides to CD4+ T helper cells [31].

MHC class II molecules are detected on APC, B lymphocytes, activated T lymphocytes, Langerhans cells, macrophages and endothelial cells [130]. In some conditions like MHC class molecules can be expressed by keratinocytes [130].

Increased reactivity of MHC II in epidermis of allergic contact dermatitis and "eczema in psoriatico" correlated with elevated number of epidermal CD4+ cells, as well as Langerhans cells in both these diseases. In comparison to allergic contact dermatitis and "eczema in psoriatico", psoriasis turned out to have less CD4+ epidermal T cells and Langerhans cells and an accordingly lower number of MHC II-positive T cells.

5.2.9 T-cell subsets: CD4+ and CD8+

T lymphocytes play a crucial role in pathogenesis of psoriasis and contact dermatitis. In both disorders, they are polarised as type 1 (CD4+ and CD8+) and as Th17. Successful therapies have been found to reduce their number [119].

T lymphocytes can be divided in CD4+ (helper T lymphocytes) and CD8+ (cytotoxic T lymphocytes). In most tissues, the ratio of CD4+CD8- to CD8+CD4- cells is about 2: 1.

In cell-mediated immunity, CD4+ T cells activate macrophages to destroy cells infected with intercellular microbes, and CD8+ T cells kill virus-infected cells. In humoral immunity, CD4+ T cells stimulate growth and differentiation of B cells [131].

Skin- associated lymphocytes are mostly located in dermis, especially perivascular and are represented by both CD4+ and CD8+ T lymphocytes. 2% of skin- associated lymphocytes reside in epidermis and belong mostly to CD8+ T cells. The expression of activation markers was observed in up to one-third of T cells [132]. It was found, that activated T lymphocytes in psoriatic skin secret cytokines such INF-γ and TNF-α [133].

Both allergic contact dermatitis and "eczema in psoriatico" showed an increased number of epidermal CD4+ and CD8+ T cells compared with psoriasis, which can be explained through lymphocytic exocytosis in epidermis.

Our results confirmed that in psoriatic dermis, CD4+ T cells outnumber CD8+ T cells (the same in the case of allergic contact dermatitis and "eczema in psoriatico"). In contrary to other authors [134,135], we did not detect the CD8+ predominance in psoriatic epidermis (in our case CD4/CD8 ratio was 1.3:1). Predominance of epidermal CD8+ T cells was observed only in the case of "eczema in psoriatico" (CD4/CD8 ratio 0.92: 1) and in healthy skin (CD4/CD8 ratio 0.75: 1).

Interestingly, "eczema in psoriatico" also had the highest count of dermal CD8+ T cells compared with allergic contact dermatitis ($p \leq 0.01$) and psoriasis ($p \leq 0.001$).

In other studies, epidermal CD8+ T cells were suggested to be a key player in the pathogenesis of psoriasis [135]. Deguchi et al. [136] examined proliferate activity of CD8+ T cells by double immunohistochemical staining (CD8/Ki67). Interestingly, CD8+ T cells with proliferating activity were located within the dermis and were not found in the epidermis. It was shown, that the number of CD8+/Ki67+ T cells in dermis in spongiotic dermatitis was significantly higher than in psoriasis. Most of the CD8+ T cells with proliferating activity were distributed in the lymphoid infiltrate in lesional dermis. It was speculated, that dermal dendritic cells could stimulate neighboring CD8+ T cells directly or via CD4+ T cells. In our study, we did not perform the double immunostaining with CD8 and Ki67. The accumulation of CD8+ T cells in the lymphoid infiltrate could suggest their proliferating activity. As already reported [136], in our observation contact dermatitis also turned out to have more dermal CD8+ positive cells than psoriasis. Surprisingly, the count of dermal CD8+ T cells in "eczema in psoriatico" outnumbered not only psoriasis, but also contact dermatitis.

These results did not differ much from those obtained from the group of patients without elevated IgE in serum. Dermal CD8+ T cells in "eczema in psoriatico" with IgE within normal range were also elevated in comparison with contact dermatitis and psoriasis, but statistically less prominent (in both cases $p \leq 0.05$).

Further examination of cytotoxic T lymphocytes is required to understand the pathomechanism of "eczema in psoriatico" better.

5.2.10 Interleukin 8 (IL-8)

Interleukin 8 is a secretory product of endothelial cells, fibroblasts and keratinocytes [137]. It is a marker of different inflammatory processes. Its reactivity was found to be increased in various inflammatory diseases like psoriasis, atopic- and contact- dermatitis [137,138]. IL-8 is known for its neutrophil activating capacity, which includes chemotaxis, degranulation and generation of toxic oxygen radicals [137].

According to literature, distribution of IL-8 varies, and has different patterns, probably due to various staining procedures [139].

Our results regarding IL-8 staining in psoriasis were consistent with Ozawa et al. [139]. IL-8 in psoriasis was detected in basal- and spinous keratinocytes as a desmosome-like pattern and in neutrophils accumulated sub- und intracorneal. Weak desmosome-like staining in basal keratinocytes was also seen in healthy controls. Surprisingly, the strongest intercellular staining in basal- and suprabasal keratinocytes was observed in allergic contact dermatitis. As expected, contact dermatitis had a weaker expression if IL-8 in stratum corneum in comparison to psoriasis, due to lower number of accumulated neutrophils. "Eczema in psoriatico" showed distinct characteristics of IL-8 staining with moderate desmosome-like patterns (less than in allergic contact dermatitis and more than in psoriasis) and moderate number of neutrophils both sub- und intracorneal (less than in psoriasis and more than allergic contact dermatitis). In our observation, IL-8 did not show positive staining of any keratinocytes in upper epidermis (consistent with results of Ozawa et al).

Desmosome-like staining of IL-8 is a finding of uncertain significance. The distribution of IL- 8 in epidermis was suggested to play a role in chemotaxis of neutrophils [139]. The enhanced reactivity of IL-8 staining in basal layers especially of contact dermatitis should be cleared and remains to be studied.

5.2.11 Interleukin 17 (IL-17)

Il-17 belongs to cell-derived proinflammatory cytokines. Recent research has demonstrated that IL-17 is not only expressed by activated memory T-cells (Th17), but also by different cells of the innate immune system, like mast cells, neutrophils, dendritic cells, γδ- T cells, macrophages and natural killer cells [140]. Lin AM. et al. have shown that mast cells are the majority of IL-17-containing cells in psoriatic skin [141], which also correlate with our observations. In our evaluation, secondly common IL-17 positive cells were neutrophils found both, in papillary dermis and in epidermal microabscesses- which reflect results of other studies [141].

IL-17 cytokine family consists of six members: IL-17A (our antibody, known also as IL-17 or CTLA-8) and IL-17B, IL-17C, IL-17D, IL-17E, IL-17F [142]. IL-17A is known to be a potent

inducer of IL-6 and IL-8 production by keratinocytes, fibroblasts and endothelial cells. These chemokines are involved in recruiting dendritic cells, Th17 cells and neutrophils. IL-17 drives the reactivity of ICAM-1 on keratinocytes. An increase of IL-17 was described in psoriasis [143-145], acute atopic dermatitis [146] and allergic contact dermatitis [143]. mRNA expression of IL-17A and IL-17F was found to be enhanced in lesional psoriatic skin, compared with nonlesional psoriatic skin [121,147-149]. It was suggested that IL-17 mRNA correlate with disease activity and therapy with cyclosporine leads to normalisation of its level [148]. Recent preliminary clinical studies show that IL-17 inhibitors are effective in psoriasis treatment [150]. IL-17 positive T cells were also found at the site of spongiosis in allergic contact dermatitis and were shown to amplify allergic reactions [151].

Our findings show an increased number of IL-17 positive cells (especially with morphology of mast cells and neutrophils) in the case of psoriasis and "eczema in psoriatico" compared to healthy skin ($p \leq 0.01$) in the whole dermis. IL-17 positive cells infiltrating dermis in allergic contact dermatitis were slightly increased compared to healthy controls, but lower than in the case of psoriasis ($p \leq 0.1$) and "eczema in psoriatico" ($p \leq 0.01$).

5.2.12 Interleukin 23 (IL-23)

IL-23 is secreted by activated dendritic cells, phagocytic cells and keratinocytes. IL-23 promotes the development and activation of Th17 cells. IL-23 plays a crucial role in the patomechanism of psoriasis. The neutralizing IL12/23p40 antibody was found to be effective in the treatment of psoriasis patient [152,153].

There are some studies describing the IL-23 cells in the lesional psoriatic skin. Wilson et al. observed an increased number of dendritic cells expressing IL-23p19 in lesional psoriatic skin [121]. Lilis J et al. [154] noted an increased number of IL-23 positive cells in the papillary dermis of plaque psoriasis, palmoplantar psoriasis and hyperkeratotic hand dermatitis compared with nonlesional psoriasis skin (no statistical differences in these groups).

In our observation, IL-23 positive cells have neutrophils´ morphology. As expected, the highest number of IL-23 positive cells was observed in psoriasis and lowest in contact dermatitis. "Eczema in psoriatico" showed similar patterns to psoriasis.

5.2.13 Interleukin 31 (IL-31)

IL-31 plays an important role in atopic dermatitis and was demonstrated to induce pruritic skin changes resembling atopic dermatitis in IL-31 over-expressing transgenic mice [155]. IL-31 was found to be up-regulated in pruritic atopic dermatitis, compared to non-pruritic psoriasis, and to healthy skin [156].

In our study, we observed an increased number of IL-31 positive cells in "eczema in psoriatico" compared to psoriasis (accordingly $p \leq 0.5$) and healthy skin ($p \leq 0.001$). Exclusion of patients with elevated IgE in serum led to other results, namely there were no statistical dif-

ferences between "eczema in psoriatico", contact dermatitis and psoriasis. It can be suggested that level of IgE in serum correlates with the number of IL-31 positive cells in dermis of the examined inflammatory diseases.

5.3 Summary

Understanding of pathomechanism of "eczema in psoriatico" was the most relevant part of this thesis. At the beginning, we performed a detailed analysis of different immunological processes in palmoplantar psoriasis and palmoplantar allergic contact dermatitis in comparison to healthy skin. In the next step, we evaluated the immunological patterns in "eczema in psoriatico" looking for similarities and differences in psoriasis and contact dermatitis.

Our study enabled a better immunohistological differentiation between psoriasis and chronic allergic contact dermatitis in palmoplantar localisation.

Our results clarified processes taking part in "eczema in psoriatico". Precise evaluation of different immunostainings revealed similar alterations in epidermal differentiations in both psoriasis and "eczema in psoriatico" (CK17, Ki67). "Eczema in psoriatico" showed contemporarily overlapping features with psoriasis (IL-8, IL-17 and IL-23) and contact dermatitis (CD1a, MHC I, MHC II, epidermal T cell subsets). Surprisingly, we discovered an increased number of dermal CD8+ T cells, in comparison not only with psoriasis, but also contact dermatitis. Elevated IgE in serum turned out to negatively influence the number of Ki67- and positively the number of CD1a- and IL-31 positive cells.
The most important results are summarised in the Figure 43.

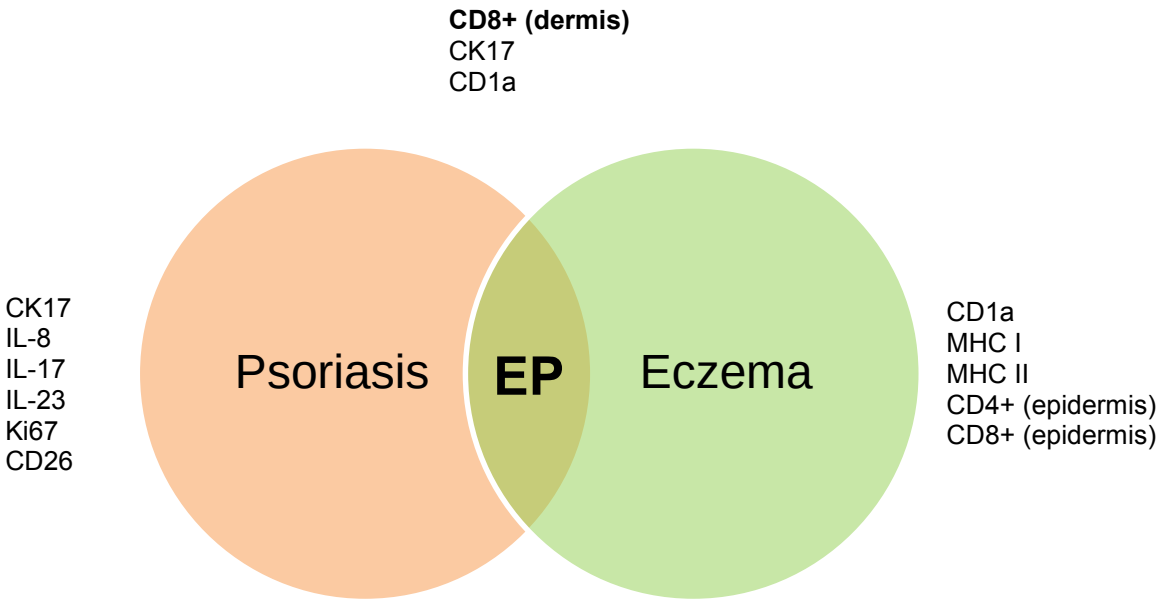

Figure 43. Results of immunohistological studies.

6. Conclusion

Scaling erythematous plaques on palms and soles often cause diagnostic difficulties. Differential diagnosis between psoriasis and chronic contact dermatitis in palmoplantar localisation is, due to overlapping clinical and histological features, hardly possible by isolated involvement.

However, proper diagnosis is important for successful therapy and discussion of occupations' triggering such conditions. Persistent palmoplantar skin changes have a big impact on life quality and may often result in long-term sickness, work-related absences and consequently on long-term unemployment.

In our observations, there is a large group of patients with erythrosquamous plaques on palms and soles that show clinical and histological features of psoriasis and contact dermatitis combined with a high frequency of positive patch tests. This constellation is mostly called "eczema in psoriatico". This separate entity encloses a major part of patients with unclear clinical and histological picture. Therefore, the focus of this thesis was to investigate a clinical, histological and immunohistological features of these patients compared to typical palmoplantar psoriasis, typical allergic contact dermatitis and healthy skin.

The first point of this work was to characterise the clinical manifestations in the different groups of patients. As most of the patients had an isolated palmoplantar involvement, final diagnosis was based on results of allergy tests and on histological and immunohistological proprieties of skin samples. In a small percentage, nail- and scalp involvement helped to favour the diagnosis of psoriasis and/or “eczema in psoriatico”. As already mentioned, patch test were positive in all patients with contact dermatitis and “eczema in psoriatico” (inclusion criteria) with metals (nickel sulfate, potassium dichromate, cobalt), balsam of Peru, fragrance mixes and formaldehyde as the most common contact allergens. Surprisingly, in more than 50% patients (5/9) with palmoplantar psoriasis, there were weak, positive patch tests results, without clinical and histological features of contact sensitisation. Strong patch reactions (≥++) were observed only in group of contact dermatitis and “eczema in psoriatico” and in no patients with palmoplantar psoriasis. Estimation of IgE levels in serum revealed elevated values in 40% of patients with psoriasis, 76.2% of patients with “eczema in psoriatico” and in only 18.2% of patients with contact dermatitis. Limitation of this test was due to the fact, that estimation of IgE in serum was not performed in all patients (in 11 of 13 with contact dermatitis, 5 of 12 with psoriasis and in 21 of 30 with “eczema in psoriatico”). Elevated IgE in serum turned out to correlate with an increased number of CD1a and IL-31 in

immunohistology.

Histologic evaluation of all slides with H&E staining was another important point of this study. "Eczema in psoriatico" turned out to have overlapping features with both psoriasis and contact dermatitis. The following features were shared with psoriasis: moderate to strong parakeratosis, regular acanthosis, loss or thinning (also partially) of granular layer, thinning of suprapapillary plates, oedema of papillary dermis and presence of Munro microabscesses. Further features of "eczema in psoriatico" were shared with contact dermatitis: neutrophils and plasma exudation in parakeratosis, lymphocytic exocytosis in epidermis, full-thickness spongiosis or formations of spongiotic vessels.

The most challenging part of the investigative studies was the performance of numerous immunohistological stainings, their quantification and comparison between all examined groups: contact dermatitis, psoriasis, "eczema in psoriatico" and healthy skin samples. It was shown that "eczema in psoriatico" has similar alternations in epidermal proliferation to psoriasis (CK17, Ki67). Due to the loss of granular layer, reduction of filaggrin staining was more pronounced in "eczema in psoriatico" than in psoriasis and contact dermatitis. CK16 turned out to be unhelpful in the differentiation of epidermal hyperproliferation in contact dermatitis, psoriasis and "eczema in psoriatico" (all samples showed similar positive reactions). Increased number of IL-8-, IL-17-, IL-23 positive cells was found in both psoriasis and in "eczema in psoriatico". Overexpression of CD1a-, MHC I- and MHC II positive cells was shared by contact dermatitis and "eczema in psoriatico". In the case of CD1a, the number of positive cells varied according to the presence of elevated IgE in serum. The evaluation of T cells subsets in epidermis revealed an elevated number of CD4+ and CD8+ T cells in both contact dermatitis and "eczema in psoriatico", which corresponded to lymphocytic exocytosis observed in H&E stains. Surprisingly, "eczema in psoriatico" showed an up-regulated number of CD8+ dermal T cells compared not only to psoriasis but also to contact dermatitis. The significance of this finding should be examined further. The density of IL-31 positive cells turned out to correlate with elevated IgE in serum und was highest in "eczema in psoriatico".

Our work provides a better understanding of not only the pathomechanism of "eczema in psoriatico", but also of psoriasis and contact dermatitis in palmoplantar localisation.

In the case of therapy resistant scaling erythema on palms and soles, we suggest detailed examination of the whole skin with its derivatives, performance of the patch tests, estimation of IgE in serum, as well as skin biopsies for further histological and immunohistological evaluation. Histologic pictures of "eczema in psoriatico" reveal psoriasiform dermatitis with lymphocytic exocytosis and spongiosis. Just with the help of single immunostainings such as CK17, CD1a and CD8, a major part of unclear cases can be classified accordingly.

This research showed that the clinical picture of palmoplantar psoriasis can be influenced markedly by coexisting contact allergy.

Summary

Psoriasis and chronic eczema at the palmoplantar sites show multiple overlapping clinical and histological features. The differentiation, especially by the lack of other skin changes is often hardly possible. In the last ten years in our department, we have observed a large group of patients with type IV-sensitisation, showing contemporarily clinical and histological features of both psoriasis and contact dermatitis. This constellation is called, in particular by us, but also occasionally in literature "eczema in psoriatico".

The purpose of the instant study was to compare clinical, histological and immunohistological characteristics of these patients with typical palmoplantar psoriasis and typical palmoplantar contact dermatitis.

Two highly experienced dermatopathologists performed a blind evaluation of 142 samples referring to psoriasis, contact dermatitis or “eczema in psoriatico“. From this collective, a final selection of 63 specimens obtained from 59 patients arose, in which both experts made a consistent diagnosis: 33 with “eczema in psoriatico”, 13 with allergic contact dermatitis and 12 with psoriasis. 5 samples of healthy skin in palmoplantar localisation were added additionally. Cases with chronic irritant non-allergic hand and foot manifestations, as well as those with isolated atopic hand dermatitis and psoriasis pustulosa palmoplantaris were excluded from this study. Hereby, we were able to generate a selective and well-defined collective for further evaluation.

Patients with positive patch tests results were assessed in parallel. The frequency of type IV sensitisation with the most common allergens was compared in relation to quality, as well as to the quantity of the reaction. Elevated IgE in serum was a common finding in the group with “eczema in psoriatico”.

To assess routine histological sections, we chose 14 parameters that according to our experience and to the literature were considered helpful in the differentiation between psoriasis from contact dermatitis. In this connection, “eczema in psoriatico” showed overlapping histological features with both diseases. The routine histological staining turned out to be insufficient for the distinction of these diseases from one another.

By immunochemistry, “eczema in psoriatico” presented similar alterations in epidermal hyperproliferation to psoriasis (CK17, Ki67). The loss of granular layer and consequently

reduction of filaggrin expression was more pronounced in “eczema in psoriatico” than in psoriasis and contact dermatitis. CK16 turned out to be of no use in the differentiation of epidermal hyperproliferation between “eczema in psoriatico“, contact dermatitis and psoriasis. “Eczema in psoriatico“revealed similarities with psoriasis in regard to the expression of IL-8, IL-17 and IL-23. An increased number of CD1a- , MHC I- and MHC II positive cells was characteristic of contact dermatitis and “eczema in psoriatico”. In both of them, lymphocytic exocytosis into epidermis could be observed, showing an elevated number of CD4+ and CD8+ T cells. Surprisingly, “eczema in psoriatico” revealed a significantly higher number of dermal CD8+ T cells than contact dermatitis and psoriasis. Elevated levels of IgE in serum correlated positively with the number of epidermal CD1a- and dermal IL-31- positive cells.

Altogether, due to some immunohistochemical constellations, „eczema in psoriatico“can be differentiated better from palmoplantar- contact dermatitis and psoriasis. The immunohistological analysis shows that in the case of specimens obtained from “eczema in psoriatico”, a small set of immunological markers specific to both diseases are found contemporaneously. Our work, therefore, provides a better understanding of the pathomechanism of psoriasis and contact dermatitis in palmoplantar localisation. In our opinion, “eczema in psoriatico“is a distinct clinical entity, and, of particular importance, with regard to occupational diseases associated with different clinical diagnostic and therapeutic consequences.

Zusammenfassung

Die Psoriasis und das chronische Kontaktekzem in palmo-plantarer Lokalisation zeigen überlappende klinische und histologische Merkmale. Häufig ist die Abgrenzung, besonders beim Fehlen typischer lokalisationsferner Hauterscheinungen schwierig. Wir haben während der letzten 10 Jahre im Patientengut unserer Klinik eine größere Gruppe von Patienten mit allergischer Typ IV-Kontaktsensibilisierung beobachtet, die sowohl klinische als auch histologische Eigenschaften einer Psoriasis und eines Kontaktekzems aufweisen. Diese Konstellation wird besonders von uns, aber auch gelegentlich in der Literatur als „Eczema in psoriatico“ genannt. Zielsetzung der vorliegenden Arbeit war es, klinische, histologische und immunohistologische Eigenschaften dieser Patienten mit palmo-plantarer Psoriasis und mit palmo-plantarem allergischem Kontaktekzem zu vergleichen.

Zwei langjährig erfahrene Dermatopathologen führten zunächst eine Blindbegutachtung von 142 Gewebeproben durch, in denen Hinweise bzw. Diagnosen für eine Psoriasis, ein Ekzem oder ein „Eczema in psoriatico“ geäußert worden waren. Aus dieser Gesamtprobe ergab sich schließlich eine aus beiden Evaluationen übereinstimmende Auswahl von 63 Biopsien von 59 Patienten, die sich von beiden Evaluierern einer Diagnose zuordnen ließ: 33 mit „Eczema in psoriatico“, 13 mit allergischem Kontaktekzem und 12 mit Psoriasis palmoplantaris. 5 gesunde Kontrollen mit gleicher Lokalisation der Hautbiopsien wurden hinzugenommen. Solche Patienten mit klinisch rein chronisch irritativer, d.h. nicht allergischer Kontaktdermatitis, solche mit isoliertem atopischem Handekzem bei atopischer Diathese bzw. atopischer Dermatitis und solche mit Psoriasis pustulosa palmo-plantaris wurden ausgeschlossen. Hierdurch konnte ein selektiertes und definiertes Kollektiv zur Evaluation herangezogen werden.

Patienten mit positiven Reaktionen im Epikutantest wurden parallel evaluiert und die Frequenz der Typ-IV Sensibilisierung mit den häufigsten Allergenen verglichen in Hinsicht auf die Qualität wie auch auf die Quantität der Reaktion. In der Gruppe der Patienten mit „Eczema in psoriatico“ wurde eine erhöhte Frequenz von IgE-Werten beobachtet.

Für die Beurteilung der routinehistologischen Parameter bzw. weiterführender Färbungen wurden 14 Parameter ausgewählt, die für die Differenzierung einer Psoriasis gegenüber

einem Kontaktekzem hilfreich sein könnten bzw. in der Literatur beschrieben wurden. Hierbei zeigte sich, dass das „Eczema in psoriatico“ überlappende histologische Merkmale beider Krankheiten aufweist und H&E Färbung nur ungenügend zur Differenzierung beiträgt.

Bei der immunohistologischen Evaluierung zeigte das „Eczema in psoriatico“ ähnliche Veränderungen in der epidermaler Differenzierung wie die Psoriasis (CK17, Ki67). Das meist fehlende Stratum granulosum konnten wir im Falle des „Eczema in psoriatico“ im Sinne einer verminderten Reduktion der Filaggrin-Expression deutlicher als bei Psoriasis und Kontaktdermatitis finden. Ein Proliferationsmarker für Keratin CK16 stellte sich nicht als hilfreich in der Differenzierung epidermaler Veränderungen zwischen Kontaktdermatitis, Psoriasis und „Eczema in psoriatico“ heraus. Das „Eczema in psoriatico“ wies hingegen Ähnlichkeiten mit einer Psoriasis in Hinsicht auf die Expression und das Muster der Expression von IL8-, IL-17 und IL-23 auf. Eine erhöhte Zahl von CD1a-, MHC I- und MHC II-positiven Zellen war charakteristisch für die allergische Kontaktdermatitis und das „Eczema in psoriatico“. In beiden klinischen bzw. histologischen Fällen wurde eine lymphozytäre Exozytose mit CD4+ und CD8+ Zellen nachgewiesen. Erstaunlicherweise fand sich jedoch beim „Eczema in psoriatico“ eine signifikant höhere Zahl von dermalen CD8+ Zellen als bei der Kontaktdermatitis oder bei der Psoriasis. Die erhöhten Serumwerte für das Gesamt-IgE korrelierten positiv mit der Zahl epidermaler CD1a- und dermaler IL-31- positiver Zellen.

Zusammenfassend kann mit Hilfe einer kleinen umschriebenen immunohistochemischen Konstellation das „Eczema in psoriatico“ allergischer Genese gegenüber der allergischen Kontaktdermatitis sowie gegenüber der normalen Psoriasis in palmo-plantarer Lokalisation besser abgegrenzt werden. Die immunohistochemischen Parameter zeigten, dass beim “Eczema in psoriatico” typische immunologische Marker der Psoriasis und Kontaktdermatitis sich gleichzeitig im Bioptat finden, aber mit wenigen anderen Merkmalen differenziert werden können. Die vorliegende Dissertation ermöglicht ein weiteres besseres Verständnis der Pathomechanismen von Psoriasis und allergischem Kontakekzem in palmoplantarer Lokalisation zu erkennen. Das „Eczema in psoriatico“ ist, unserer Meinung nach, eine klinische Entität, die darüber hinaus von besonderer gutachterlicher Bedeutung bei Berufsdermatosen ist, sowie auch eine andere therapeutische Konsequenz nach sich zieht.

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Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promo-tion eingereichte Dissertation mit dem Titel

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in der Klinik für Dermatologie und Venerologie

mit Unterstützung durch
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ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

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Ich habe diese Dissertation bisher an keiner in- oder ausländichen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

Magdeburg, den 10.04.2014

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