

CME

Autoimmune bullous skin diseases.

Part 1: Clinical manifestations

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Summary

Autoimmune bullous skin diseases are characterized by autoantibodies against adhesion molecules of the skin. Pemphigus is a disorder with an intraepidermal loss of adhesion and is characterized by fragile blisters and erosions. Pemphigus vulgaris often shows extensive lesions of the oral mucosa, while pemphigus foliaceus is commonly restricted to cutaneous involvement with puff pastry-like scale formation. Paraneoplastic pemphigus is obligatorily associated with malignancies and often presents as hemorrhagic stomatitis with multiforme-like exanthems. IgA pemphigus typically presents with pustules and annular plaques but not with mucosal involvement. The clinical spectrum of the pemphigoids includes tense blisters, urticarial plaques, and prurigo-like eczematous lesions. Pemphigoid gestationis mostly occurs during the last trimester of pregnancy and mucous membrane pemphigoid primarily involves the oral mucosa and conjunctivae and leads to scarring. Linear IgA bullous dermatosis manifests with tense blisters in a “cluster of jewels”-like pattern in childhood and is more heterogeneous in adulthood. Classical epidermolysis bullosa acquisita shows extensive skin fragility. Dermatitis herpetiformis is associated with gluten-sensitive enteropathy and manifests clinically with severe itching and papulovesicles on the extensor surfaces of the extremities and the lumbosacral area. The intention of the review is to demonstrate the heterogeneous clinical spectrum of autoimmune bullous disorders.

Pemphigus is characterized by the production of autoantibodies against desmosomal structure proteins, which results in a loss of intraepidermal adhesion.

1 Clinical manifestations

1.1 Diseases with intraepidermal loss of adhesion

Pemphigus is characterized by the production of autoantibodies against desmosomal structure proteins. This results in a loss of intraepidermal adhesion (Figure 1); this corresponds to the clinical features of blisters and erosions of skin and mucous membranes. The typical blistering gave the disease its name, “pemphigus” stems from the Greek word *pemphix* for “blister”.

1.1.1 Pemphigus vulgaris

Pemphigus vulgaris (from the Latin word *vulgus* „common“) is the most frequent representative of the group of pemphigus diseases with an incidence of 0.1–0.5/100 000 population. In certain ethnic groups, especially the Jewish population, but also in Mediterranean countries, a distinctly higher prevalence is reported. There exists a genetic predisposition for developing pemphigus vulgaris; among those affected HLA types HLA-DRB1*0402 and HLA-DQB1*0503 occur more frequently. The disease

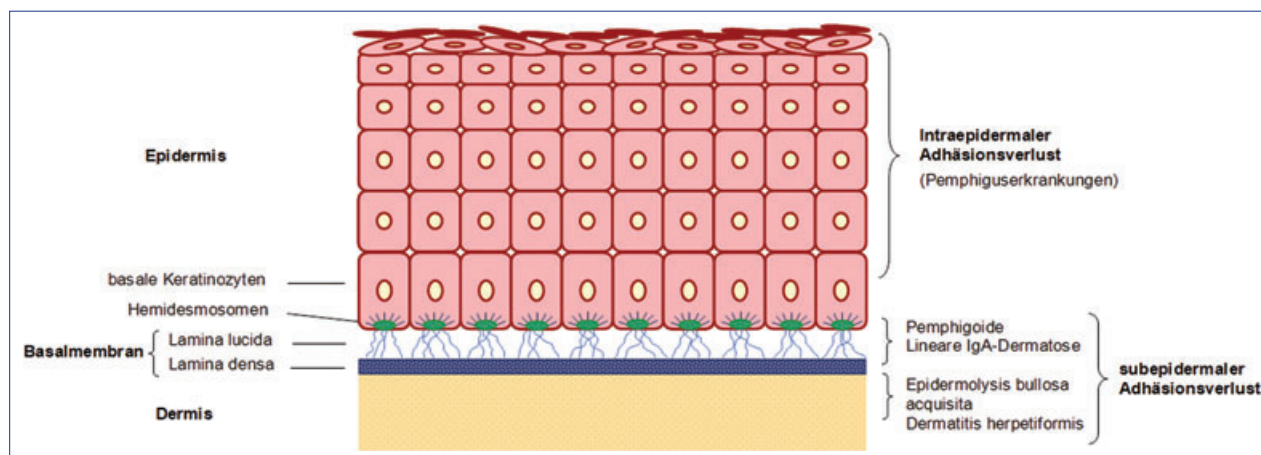


Figure 1: Skin structure and site of loss of adhesion in autoimmune bullous diseases. Schematic representation of the epidermis and dermis with site of adhesion loss of the different autoimmune bullous skin disorders.

manifests particularly during middle age with an age peak between the 4th and 6th decade of life, but may even occur in the elderly or children.

Initial signs and symptoms of pemphigus vulgaris in over 70 % of cases are highly painful and long-persisting erosions of the mucous membranes, especially of the oral mucosa [1]. The disease is often not recognized for a long time in this stage and other diagnoses are suspected such as e. g. herpes stomatitis, recurrent aphthae or even candida stomatitis resulting in the corresponding therapy attempts over long periods of time that remain frustrating. Therefore pemphigus vulgaris should be included in the differential diagnostic consideration in the event of long-standing mucous membrane lesions and complete inspection of the patients be performed. Involvement of other mucous membranes is possible, e. g. nasal, laryngo-esophageal, genital, anal and conjunctival (Figure 2a–f). On the skin pemphigus vulgaris manifests as flaccid blisters and extensive weeping and in the further course crusted bright red erosions. Due to the fragility of the blisters they can in many case no longer be identified. Cutaneous lesions can occur on the entire skin surface; mechanically strained and intertriginous sites are nonetheless favored (Figure 2g–j). Even localized skin involvement, e. g. on

Initial signs and symptoms of pemphigus vulgaris are persistent erosions of the oral mucosa.

Pemphigus vulgaris is characterized by flaccid blisters and extensive weeping erosions.



Figure 2: Pemphigus vulgaris. Mucosal involvement (a–f): erosions of gingiva (a, b), buccal mucosa (c), tongue (d), hard palate (e), conjunctiva (f). Skin involvement (g–j): crusty erosions of face (g), trunk (h), scalp (i), paronychia (j).



Figure 3: Pemphigus subgroups. Pemphigus vegetans (a): livid intertriginous erythema evolving into papillomatous vegetating plaques. Atypical pemphigus (b, c): annular scaling plaques. Paraneoplastic pemphigus (d–f): hemorrhagic stomatitis (d), extensive weeping erosions on the trunk (e, f). IgA pemphigus (g–i): pustules and collarette-like scaling on the trunk.

During the active phase of pemphigus vulgaris both Nikolsky signs can be elicited.

In neonatal pemphigus, crusted erosions develop as a transient phenomenon.

Pemphigus vegetans is characterized by the development of papillomatous and verrucous vegetations with a predilection for intertriginous sites.

the scalp, is possible. On the whole, without treatment the lesions hardly have a tendency to heal and are highly painful. In case of lesions resistant to therapy secondary herpes infection should be considered as an aggravating factor [2]. Due to secondary complications such as e. g. infections or nutritional deficiency, pemphigus vulgaris was associated with high lethality in the past.

During the active phase of pemphigus vulgaris both Nikolsky signs can be elicited. The direct Nikolsky sign describes the phenomenon that on clinically inconspicuous perilesional skin tangential pressure can cause the epidermis to separate from the dermis. An additional less specific clinical sign is the indirect Nikolsky sign, where an intact blister can be shifted laterally and enlarged by digital pressure.

If women with active pemphigus become pregnant the newborn may develop what is termed *neonatal pemphigus* due to the transplacental transmission of pemphigus autoantibodies. Here, exanthematous, crusted erosions develop as a transient phenomenon over several weeks until the maternal autoantibodies are degraded.

In addition to classical pemphigus vulgaris numerous special forms exist. *Pemphigus vegetans* is characterized by a predilection for intertriginous as well as anogenital and nasolabial sites. Blisters and pustules appear that in the course of time transform into extensive erosive defects (Figure 3a). Pemphigus vegetans received its name from the marked tendency for the development of papillomatous and verrucous vegetations. Mucous membrane involvement is frequent. Depending on the clinical course two types of pemphigus vegetans are differentiated. The Neumann type takes an aggressive course with the formation of whitish, macerated plaques, while in the Hallopeau type initially pustules appear that transform into warty lesions. An intense fetid odor is present [3, 4].

Pemphigus herpetiformis is a rare variant of pemphigus vulgaris in which grouped vesicles appear on reddish plaques. In part these can resemble urticaria, oral mucosa

involvement is rare. Pemphigus herpetiformis therefore possesses clinical similarity to dermatitis herpetiformis and must be included in the differential diagnostic considerations.

1.1.2 Pemphigus foliaceus

In contrast to pemphigus vulgaris in pemphigus foliaceus (from the Latin *folium* “leaf”) there is exclusive involvement of cornified skin. Often initial circumscribed lesions appear in seborrheic areas such as the scalp as well as the presternal and interscapular regions. First flat, fragile blisters appear slowly. In the further course hyperkeratotic scales develop; on the face they may be distributed in a butterfly-like pattern over nose and cheeks (Figure 4a–d). Due to the lack of oral mucosa involvement, the prognosis of pemphigus foliaceus is usually more favorable than that of pemphigus vulgaris. Nonetheless, due to the extensive weeping erosions there is a danger of superinfection with the development of secondary pyoderma up to sepsis. In cases of erythroderma of unknown origin, pemphigus foliaceus must be considered as a possible cause, as in some cases the extensive exfoliation may resemble erythroderma. Drugs, sunlight or malignancies have been reported as possible triggers of pemphigus foliaceus.

Pemphigus seborrhoicus is a special variety of pemphigus foliaceus. Here, due to the very superficial blistering extensive erythematous plaques and erosions develop in seborrheic areas (Figure 4e).

In pemphigus foliaceus fragile blisters develop and evolve into hyperkeratotic scales; there is no oral mucosa involvement.

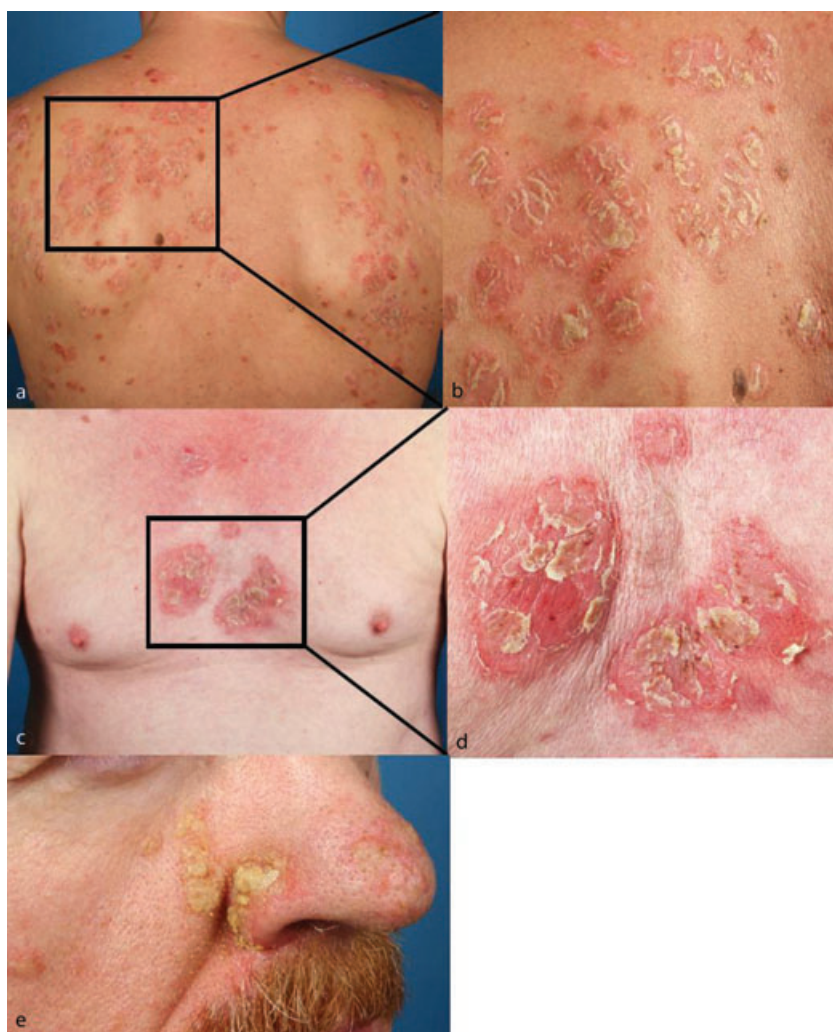


Figure 4: Pemphigus foliaceus. Preferential involvement of seborrheic areas (a, c), scale formation, crusts and hyperkeratosis (b, d). Special variant (e): Pemphigus seborrhoicus with extensive superficial, crusted plaques of the seborrheic areas.

Fogo selvagem is an endemic variant of pemphigus foliaceus.

Pemphigus erythematosus resembles cutaneous lupus erythematosus clinically.

Paraneoplastic pemphigus usually manifests initially as hemorrhagic stomatitis as well as blisters with predilection for the upper trunk and erythema multiforme-like lesions.

Paraneoplastic pemphigus is an obligatory paraneoplastic marker, so a comprehensive work-up is needed.

A feared complication of paraneoplastic pemphigus is obliterating bronchiolitis.

Drugs with sulfhydryl groups such as e. g. captopril or D-penicillamine are triggers of drug-induced pemphigus. Clinically it resembles pemphigus foliaceus.

IgA pemphigus is characterized by fragile blisters and pustules as well as annular plaques with accentuated margins and collarette-like scaling.

An endemic variant of pemphigus foliaceus is *fogo selvagem*, from the Portuguese *fogo* “fire” and *selvagem* “wild”. The erosions are intensely painful like “wild fire”. Fogo selvagem affects predominantly young women in endemic regions (Lima Verde) in Brazil; further endemic forms are found in North Africa (especially Tunisia). Here, too, erythroderma is possible, and microbial antigens are discussed as possible triggers [5].

Another special form of pemphigus foliaceus is *pemphigus erythematosus* (Senear-Usher). Clinical features resemble cutaneous lupus erythematosus with superficial erosions, erythemas and hyperkeratoses. In about 80 % of cases antinuclear antibodies in the medium titer range can be detected, usually in a homogeneous pattern without the presence of anti-ds-DNA antibodies. Pemphigus erythematosus affects mainly older patients and here, too, drugs and sunlight but also trauma are considered possible triggers [6].

In recent times clinical variants of pemphigus have been reported that clinically possess herpetiform, in part vegetating features with positive direct and indirect immunofluorescence microscopy, but where the classical IgG autoantibodies against desmogleins cannot be detected. This clinically heterogeneous special form is therefore termed *atypical pemphigus*. Oral mucosa involvement is frequent (Figure 3b, c).

1.1.3 Paraneoplastic pemphigus

Paraneoplastic pemphigus is a pemphigus form associated with tumors taking a clinically dramatic course. Paraneoplastic pemphigus typically manifests initially as hemorrhagic stomatitis with extensive mucous membrane erosions with intense pain and resistance to therapy. Polymorphic clinical features include blisters with predilection for the upper trunk as well as lichenoid palmo-plantar exanthems; sometimes erythema multiforme-like lesions resembling toxic epidermal necrolysis are present [7, 8] (Figure 3d–f). Paraneoplastic pemphigus is almost always associated with obvious or occult neoplasias. Cross-reactivity with tumor antigens are discussed as possible pathomechanism of paraneoplastic pemphigus. Lymphoreticular malignancies (e. g. B-cell lymphomas) predominate, more rarely is paraneoplastic pemphigus associated with benign tumors (e. g. thymomas, Castleman lymphomas). It is important to note that paraneoplastic pemphigus may precede the manifestation of the malignancy. Therefore, when paraneoplastic pemphigus is suspected clinically, a comprehensive work-up is mandatory. After remission of the basic disease improvement of clinical findings is possible. Involvement of the pulmonary epithelium as obliterating bronchiolitis, which is associated with intrapulmonary bleeding and a lethality of 30 %, is feared [9]. Due to the involvement of diverse organ systems paraneoplastic pemphigus has recently often been viewed as a mucocutaneous variant of the “paraneoplastic autoimmune multiorgan syndrome” (PAMS) [10].

1.1.4 Drug-induced pemphigus

Particularly drugs with sulfhydryl groups such as e. g. captopril, D-penicillamine or piroxicam are triggers of drug-induced pemphigus [11]. Particularly when triggered by drugs with sulfhydryl group drug-induced pemphigus shares clinical features with pemphigus foliaceus; rarely is oral mucosa involved. After discontinuation of the responsible medications cutaneous lesions may heal spontaneously, nevertheless, frequently therapy appropriate to pemphigus is needed.

1.1.5 IgA pemphigus

IgA pemphigus is a rare entity among the pemphigus diseases. Two types are differentiated, the *intraepidermal neutrophilic dermatosis* and the *subcorneal pustular dermatosis*. IgA pemphigus is characterized by fragile blisters and pustules on erythematous, scaling skin with favoring of the distal trunk and proximal limbs as well as intertriginous sites. The lesions have a distinct tendency to coalesce, so that clinically often annular infiltrated plaques with accentuated margins and collarette-like scaling are seen (Figure 3g–i). Mucosal involvement is rare. An association of IgA pemphigus with monoclonal IgA gammopathies and inflammatory bowel diseases (e. g. Crohn disease, ulcerative colitis) but also autoimmune diseases such as Sjögren syndrome and rheumatoid arthritis have been reported.

1.2 Diseases with subepidermal loss of adhesion

1.2.1 Bullous pemphigoid

Bullous pemphigoid is the most common bullous autoimmune dermatosis. In recent prospective studies from Germany and Switzerland the annual incidence was about 12 to 13 new cases per 1 million population [12, 13]. It is primarily a disease of the elderly with an incidence among patients aged over 90 years being 40 per 100 000 population per year. Overall men are somewhat more frequently affected than women. Bullous pemphigoid usually presents with pleomorphic clinical features. Initially what is termed the premonitory stage is characteristic. Here, over a time period of weeks to months highly pruritic eczema-like or urticarial erythemas, initially without blistering, appear (5d, e). Therefore, in the event of long-persisting, highly pruritic eczema-like or urticarial or erythematous skin lesions in elderly patients bullous pemphigoid should be included in the differential diagnostic considerations. Following the premonitory stage tense blisters with serous or rarely even hemorrhagic content appear in phases (Figure 5a–c). Usually the lesions appear on an erythematous base and severe pruritus is present [14]. Due to subepidermal blistering

Bullous pemphigoid is the most common bullous autoimmune dermatosis. It occurs primarily in the elderly.

The premonitory stage presents with highly pruritic eczema-like or urticarial erythemas without blistering.



Figure 5: Bullous Pemphigoid. Tense blisters, crusts and erosions on an erythematous base, favoring of the intertriginous and seborrheic areas (a, b). Tense blisters on lateral fingers (c). Premonitory pemphigoid with urticarial exanthema (d, e). Partly annular urticarial erythema and eczema-like appearance on the trunk and extremities (f). Manifestation on the hard and soft palate (g). Prurigo-like bullous pemphigoid with excoriated papules on the trunk and extensor surface of the extremities (h, i).

Fully developed bullous pemphigoid displays tense blisters on an erythematous base in the presence of severe pruritus.

Prurigo-like bullous pemphigoid presents with erythematous papules with central, excoriated vesicles.

Pemphigoid gestationis manifests as grouped, urticarial papules and plaques, in part in the form of target lesions, usually in a periumbilical distribution.

The first manifestation of pemphigoid gestationis is usually between the 2nd and 3rd trimester, sometimes even in the postpartal period.

Occasionally there is transient appearance of erythematous plaques and blisters in the newborn.

In mucous membrane pemphigoid blisters appear on mucous membranes and skin that heal with a defect resulting in the formation of scars, strictures and synechiae.

Ocular involvement results in blindness in 20 % of cases.

The blisters are in contrast to the pemphigus diseases extremely stable, as the roof of the blister consists of the entire epidermis (Figure 1). Sometimes blistering starts on palmoplantar skin or on the lower legs as well as favoring intertriginous sites. The indirect Nikolsky sign is always positive; the direct Nikolsky sign can be elicited only on perilesional skin. During the course, erosions and crusts form. In about 10–30 % there is involvement of oral mucous membranes, usually in the form of erosions, more rarely even as blistering (Figure 5g). Further clinical variants of bullous pemphigoid can manifest resembling eczema, urticaria (Figure 5f) or prurigo simplex subacuta in the form of erythematous papules with central, usually excoriated vesicles. The latter is also termed *prurigo-like bullous pemphigoid* (Figure 5h, i). Further special variants are *localized bullous pemphigoid*, which usually occurs in an isolated fashion on the lower leg or neck and resembles bullosis diabetorum clinically. In *vegetating bullous pemphigoid* purulent, verruciform and crusted lesions in intertriginous areas occur. *Dyshidrosiform pemphigoid* usually occurs on palmoplantar skin and *vesicular bullous pemphigoid* resembles dermatitis herpetiformis clinically. Altogether bullous pemphigoid takes a chronic course in phases. Certain drugs (e. g. salazosulfapyridine, penicillin V, diazepam, diuretics [furosemide], ACE inhibitors, NSARD, gold preparations, sulfonamide, penicillamine, isoniazid), UV radiation or even x-rays have been reported as triggers. Bullous pemphigoid has often been associated with malignancies, but the relationship is controversial. With increasing age, the incidence of both bullous pemphigoid and many malignancies rises.

1.2.2 Pemphigoid gestationis

Pemphigoid gestationis is a further disease of the pemphigoid group occurring in one out of about 40 000–50 000 pregnancies. After a non-specific prodromal phase with generalized pruritus, grouped, urticarial papules and plaques, in part in the form of target lesions, appear usually in a periumbilical distribution. Due to the grouped distribution of lesions pemphigoid gestationis was formerly also termed “herpes gestationis”. During the course vesicles may appear, but cases without blistering are possible. Also manifestations on the limbs, especially on hands and feet, are not rare. (Figure 6a–c). Overall, features are polymorphous; in about 20 % of cases there is mucous membrane involvement. The first manifestation of pemphigoid gestationis is usually between the 2nd and 3rd trimester, sometimes even in the postpartal period [15]. Usually pemphigoid gestationis takes a self-limited course with spontaneous healing within several weeks after delivery. Upon renewed administration of hormonal contraceptive agents, start of the menstrual cycle or subsequent pregnancies recurrences can occur. In further pregnancies often more severe courses and an earlier manifestation of cutaneous lesions are observed. Further, pemphigoid gestationis can occur in association with choriocarcinoma or hydrated mole. Therefore, in case of persistence of skin lesions close gynecological control should be instituted.

In addition, the development of placental insufficiency and underweight newborns is favored and there is an increased rate of prematurity, so that careful monitoring of pregnancy is recommended. In 5–10 % of all cases there is passive transplacental transmission of maternal IgG autoantibodies with the transient appearance of erythematous plaques and blistering in the newborn. A dependency on HLA types has also been reported (HLA-DR3 and HLA-DR4 in the mother, HLA-DR2 in the father). As the risk of recurrence with the same father is increased, the production of antibodies against paternal HLA antigens of the placenta is discussed as a possible cause of pemphigoid gestationis.

1.2.3 Mucous membrane pemphigoid

Mucous membrane pemphigoid affects predominantly older people and is characterized by recurrent blistering of mucous membranes, but also the skin. With the formation of scars, strictures and synechiae healing is with a defect. In 75 % of cases there is involvement of the oral mucous membranes. Initially this presents as desquamative gingivitis; recurrent blistering finally leads to healing with scarring. Irreversible damage of the periodontium with consecutive tooth loss is possible. In contrast to mucous membrane lesions in pemphigus vulgaris only little pain exists. Ocular involvement usually starts unilaterally with clinical features of conjunctivitis, in the further course scarring leads to stricture, entropion, trichiasis, synechiae and cornea atrophy



Figure 6: Additional bullous disorders with subepidermal loss of adhesion. Pemphigoid gestations (a–c): polymorphic appearance accentuating the lower abdomen (a) and the extremities (b), centrally erosive plaques with multi-forme-like appearance (c). Mucous membrane pemphigoid (d, e): conjunctivitis with fibrin layers and incipient synechiae. Lichen ruber pemphigoides (f): coincidence of lichenoid papules and tense blisters. Dermatitis herpetiformis (g–i): excoriated papules on the extensor surface of the extremities.

(Figure 6d, e) [16]. In 20 % of cases blindness ensues. Nasopharyngeal involvement manifests as ulcerations, epistaxis, obstruction, dysphagia as well as stenoses. In the anogenital region scarring and synechiae are seen. In men adhesion between glans penis and preputium can develop, in women obstruction of the introitus vaginae. Therapeutically additional surgical measures on the mucous membranes are often required e. g. surgical lysis of symblephara or entropions on the eye or dilatation of esophageal strictures. In 20–30 % of cases skin involvement is also present in mucous membrane pemphigoid. Clinically this resembles bullous pemphigoid with generalized blistering, but can also occur in a localized manner on the scalp or upper trunk. Healing with atrophic scars is frequent, which can lead to scarring alopecia on the scalp. Cutaneous lesions often demonstrate a tendency for rapid remission, on the whole, nevertheless, mucous membrane pemphigoid is distinctly refractory to treatment. *Brunsting-Perry pemphigoid* is a variant of mucous membrane pemphigoid and occurs especially in elderly men. Usually there is solitary involvement of the head, forehead and nape of the neck with blisters and subsequent atrophy and scarring. Further, it should be noted that in a subtype of mucous membrane pemphigoid, anti-laminin 332 (epiligrin) pemphigoid, an association with malignancies has been reported in 30 % of cases, so that the appropriate screening examinations should be arranged for [17].

Anti-laminin 332 (epiligrin) pemphigoid is associated with malignancies in 30 % of cases.

1.2.4 Lichen planus pemphigoides

Characteristic for lichen planus pemphigoides is that clinical features both of lichen planus with polygonal, livid papules, as well as of bullous pemphigoid are present. Lichen planus usually manifests before the start of blistering. In contrast to bullous lichen planus blisters in lichen planus pemphigoides occur both on lichenoid lesions as well as on unaltered skin (Figure 6f). Triggering by drugs has been reported. It is questionable if this represents an independent disease entity or more likely the transition of chronic lichen planus into bullous pemphigoid.

Laminin γ 1 pemphigoid is frequently associated with psoriasis.

1.2.5 Anti-laminin γ 1 pemphigoid

Laminin γ 1 pemphigoid (formerly anti-p200 pemphigoid) is a rare disease of the pemphigoid group that occurs especially in middle age. It features erythematous plaques and tense blisters on the trunk as well as palms and soles. Clinically there is a resemblance to dermatitis herpetiformis. Usually there is severe pruritus and in 20 % there is simultaneous mucous membrane involvement. Typical is the association with psoriasis, that is observed in 40 % of cases [18].

Linear IgA dermatosis is the most common autoimmune bullous disorder of childhood.

1.2.6 Linear IgA dermatosis

Several age peaks have been described for linear IgA dermatosis. It represents the most common autoimmune bullous disorder of childhood with age peak of 4–5 years. In adulthood it usually manifests between the 20th and 40th year of life, a further age peak is found above age 60. Overall, clinical features of linear IgA dermatosis correspond to a mixture of dermatitis herpetiformis and bullous pemphigoid. Only a few decades ago was linear IgA dermatosis differentiated from dermatitis herpetiformis as an own entity. Predilection sites of linear IgA dermatosis are the trunk with iliosacral accentuation, further regions such as e. g. legs, face or large body folds can also be affected. Typically, pearl necklace-like grouped, centrifugally arranged tense blisters, erythema and urticarial plaques are present and severe pruritus exists (Figure 7a–d) [19]. Especially in children a “jewel-like” distribution of blisters exists (“cluster of jewels”) (Figure 7g, g) [20]. Also annular, garland-like or multiforme-like lesions can occur. In 50 % there is mucosal involvement, especially of the oral mucous membranes (Figure 7e). In the event of conjunctival involvement healing with scarring can take place. In individual cases an association with malignancies as well as hematological disease (chronic lymphatic leukemia) has been reported; ulcerative colitis and primary sclerosing cholangitis can also occur as rare concomitant diseases. Further, medications as trigger have been reported, e. g. vancomycin, lithium, less frequently diclofenac, captopril, cephalosporins, glibenclamide, iodine, penicillin, interferon- γ as well as cytostatic agents.

Linear IgA dermatosis presents with tense blisters in a pearl necklace-like arrangement (termed “cluster of jewels”; especially in children) and urticarial plaques. In 50 % there is mucosal involvement.

1.2.7 Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita represents a further, rare autoimmune bullous dermatosis. The disease presents in three clinical variants. The classical variant is the *mechanobullous, noninflammatory form*, in which distinct fragility of the skin stands in the foreground [21]. Even slight trauma elicits blistering and erosions of the skin. Sites of predilection are mechanically stressed areas such as hands and feet, but also elbow and knee. Healing of lesions leaves atrophy, milia, scars as well as pigmentation disorders. Severe cases are characterized by fibrosis of hands and feet. Nail dystrophy is possible; on the scalp scarring alopecia can develop. Often there is involvement of the oral mucosa in the form of hemorrhagic erosions that can atrophy during the course (Figure 8). Extracutaneous involvement, e. g. of esophagus or urethra, is rare, but can lead to strictures. A further variant is the *generalized inflammatory form* of epidermolysis bullosa acquisita that clinically resembles bullous pemphigoid. This form is characterized by tense blisters usually on an erythematous base. The third, *localized variant* usually presents on the mucous membranes and bears clinical resemblance to mucous membrane pemphigoid.

In the most frequent mechanobullous, noninflammatory form of epidermolysis bullosa acquisita distinct skin fragility exists.

At mechanically stressed skin sites atrophies, milia and scars form. Often there is involvement of the oral mucous membranes.

The first manifestation of epidermolysis bullosa acquisita is possible at any age with a peak incidence between age 40 and 60. Epidermolysis bullosa acquisita is possible even in children. Here clinical features are heterogeneous similar to childhood linear IgA dermatosis, childhood bullous pemphigoid and the congenital epidermolysis



Figure 7: Linear IgA bullous Dermatitis. Annular lesions with marginal “cluster of jewels” (a–d): accentuation of the truncal areas (a, b), face (c), lumbosacral located excoriated papules resembling dermatitis herpetiformis (d). Involvement of the gingiva (e). Chronic bullous disease of childhood with distinct “cluster of jewels” (f, g).

bullosa forms. For epidermolysis bullosa acquisita an association with malignancies and other autoimmune diseases (e. g. lupus erythematosus, rheumatoid arthritis, Crohn disease) has been reported.



Figure 8: Epidermolysis bullosa acquisita – mechanobullous variant. Extensive erosions of the trunk (a) and scalp (b). Mucosal involvement (c–e): tongue (c), palate (d), lower lip mucosa (e). Tense blisters and erosions on trauma-prone skin areas, nail dystrophy, fibrosis (f–h).

1.2.8 Dermatitis herpetiformis

Dermatitis herpetiformis, also termed Duhring disease, can manifest at any age, but often has its onset between the age of 25 and 55 years. Men are affected almost double as frequently as women. The annual incidence demonstrates great regional differences and in Germany (Lower Franconia) is 1 new case per 1 million population per year [12, 22], while the annual incidence in a recent Finnish study is 35 new cases per 1 million population [23]. Cardinal symptom is often agonizing, burning to stinging pruritus. Often suddenly itching or burning, urticarial erythemas, but also grouped “herpetiform” papules and vesicles appear. Clinical features are on the whole polymorphous with vesicles, wheals, papules, erosions, excoriations and scars; rarely eczematous cutaneous lesions and large blisters occur. There is usually symmetrical,

Cardinal symptom of dermatitis herpetiformis is agonizing, burning pruritus.

Clinical features are polymorphous with vesicles, wheals, papules and erosions.

disseminated skin involvement. Sites of predilection are the upper shoulder, iliosacral and gluteal regions, further the extensor surfaces of the extremities with accentuation of elbows and knees as well as the scalp (Figure 6g–i). Rarely is there involvement of the oral mucous membranes [24]. Dermatitis herpetiformis is considered the cutaneous manifestation of gluten-sensitive enteropathy, with the enteropathy also being clinically manifest in only 10–20 % of cases. Nonetheless, mucosal biopsies often reveal jejunum atrophy. Dermatitis herpetiformis in childhood behaves differently; it is usually associated with clinically manifest celiac disease. Dermatitis herpetiformis is often associated with other autoimmune diseases such as e. g. autoimmune thyroiditis, vitiligo, type I diabetes as well as pernicious anemia. Further, HLA association exists (HLA-DR3, DQB1*0302, HLA-DQ2). Oral administration of iodine for provocation of a disease flare – as practiced in the past – is obsolete today. Characteristic is the rapid improvement of pruritus after administration of diaminodiphenylsulfone (dapsone). In about 10 % of cases spontaneous remissions also occur.

Sites of predilection are the upper shoulder, iliosacral, gluteal regions as well as the extensor surfaces of the extremities, especially elbows and knees.

Dermatitis herpetiformis is considered the cutaneous manifestation of gluten-sensitive enteropathy.

Conflicts of interest

None.

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Fragen zur Zertifizierung durch die DDA

1. Welche Aussage zum Pemphigus vulgaris trifft zu?

- a) Die Mundschleimhautläsionen beim Pemphigus vulgaris sind stets schmerzfrei.
- b) Der Pemphigus vulgaris ist die häufigste blasenbildende Autoimmundermatose.
- c) Der Hautbefall beim Pemphigus vulgaris ist stets generalisiert.
- d) Unbehandelt besteht eine hohe Letalität.
- e) Eine sekundäre Herpesinfektion kommt nur selten vor.

2. Welche Aussage trifft zu? Der Pemphigus foliaceus ...

- a) ist meist extremitätenbetont.
- b) zeigt häufig eine Mundschleimhautbeteiligung.
- c) kann sich als Erythrodermie manifestieren.
- d) kommt als endemische Variante vor allem in Asien vor (Fogo selvagem).
- e) ist häufig mit anti-ds-DNA-Antikörpern assoziiert (Pemphigus erythematosus).

3. Welche Aussage zum paraneoplastischen Pemphigus trifft **nicht** zu?

- a) Der paraneoplastische Pemphigus kann sich in Form von lichenoiden Palmoplantarekzemen äußern.
- b) Der paraneoplastische Pemphigus ist in 50 % der Fälle mit einer Tumorerkrankung assoziiert.
- c) Die obliterierende Bronchiolitis als Komplikation des paraneoplastischen Pemphigus hat eine Letalität von 30 %.
- d) Der paraneoplastische Pemphigus kann auch mit gutartigen Tumoren assoziiert sein.
- e) Initial liegen meist flächige, schmerzhafte Schleimhauterosionen vor.

4. Welche Aussage trifft zu?

- a) Als Auslöser für den medikamenteninduzierten Pemphigus sind ausschließlich Medikamente mit Sulfhydrylgruppe beschrieben.
- b) Beim medikamenteninduzierten Pemphigus liegt häufig eine Schleimhautbeteiligung vor.
- c) Der IgA-Pemphigus ist durch pralle Blasen gekennzeichnet.
- d) Der IgA-Pemphigus kann mit einer Colitis ulcerosa assoziiert sein.
- e) Der atypische Pemphigus weist selten eine Mundschleimhautbeteiligung auf.

5. Welche Aussage trifft zu? Das bullöse Pemphigoid ...

- a) kann sich initial in Form von juckenden Erythemen äußern.
- b) ist stets mit einer malignen Grunderkrankung assoziiert.
- c) hat einen Altersgipfel zwischen 50 und 60 Jahren.
- d) weist stets eine Blasenbildung auf.
- e) zeigt nie eine Mundschleimhautbeteiligung.

6. Welche Aussage trifft zu? Das Pemphigoid gestationis ...

- a) kommt nur bei Schwangeren vor.
- b) kann zu transienten Hautveränderungen beim Neugeborenen führen.
- c) tritt in der Regel in der Frühschwangerschaft auf.
- d) ist stets mit einer Herpesinfektion assoziiert.
- e) tritt vor allem bei Raucherinnen auf.

7. Welche Aussage trifft **nicht** zu?

- a) Die Augenbeteiligung beim Schleimhautpemphigoid kann zur Erblindung führen.
- b) Beim Schleimhautpemphigoid liegt nie eine Hautbeteiligung vor.
- c) Das anti-Laminin- γ 1-Pemphigoid kann mit einer Psoriasis assoziiert sein.

- d) Die lineare IgA-Dermatose ist die häufigste blasenbildende Autoimmundermatose im Kindesalter.
- e) Die lineare IgA-Dermatose weist in 50 % aller Fälle eine Schleimhautbeteiligung auf.

8. Welche Aussage trifft zu? Die Epidermolysis bullosa acquisita ...

- a) zeigt nur selten eine Schleimhautbeteiligung.
- b) kommt im Kindesalter nicht vor.
- c) kann zur Milienbildung führen.
- d) äußert sich häufig durch Pustelbildung.
- e) tritt nie an den Extremitäten auf.

9. Welche Aussage trifft **nicht** zu? Die Dermatitis herpetiformis ...

- a) äußert sich häufig durch brennenden Juckreiz.
- b) gilt als kutane Manifestation der glutensensitiven Enteropathie.
- c) manifestiert sich nur an den seborrhoischen Arealen.
- d) kann durch Gabe von Jod provoziert werden.
- e) kann mit einer perniziösen Anämie assoziiert sein.

10. Welche Aussage trifft zu?

- a) Beim paraneoplastischen Pemphigus können verschiedenste Organsysteme beteiligt sein.
- b) Der Pemphigus herpetiformis ist stets mit einer Herpesinfektion assoziiert.
- c) Unter Einwirkung von UV-Strahlung kommt es stets zur Besserung von Pemphigusläsionen.
- d) Die Nikolski-Phänomene lassen sich bei allen blasenbildenden Autoimmundermatosen nachweisen.
- e) Der Pemphigus vegetans heilt stets unter Milienbildung ab.

Liebe Leserinnen und Leser,

der Einsendeschluss an die DDA für diese Ausgabe ist der 18. November 2011.

Die richtige Lösung zum Thema „Klinische Langzeit-Studien: Erfassen und Interpretieren von Daten“ in Heft 6 (Juni 2011) ist: 1d, 2a, 3e, 4e, 5b, 6c, 7d, 8a, 9b, 10c.

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