Autoimmune blistering diseases

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Pemphigus

Pemphigus vulgaris
Pemphigus foliaceus
Paraneoplatic pemphigus

intraepidermal blister formation

Pemphigoid

Bullous pemphigoid
Mucous membrane pemphigoid
Pemphigoid gestationis

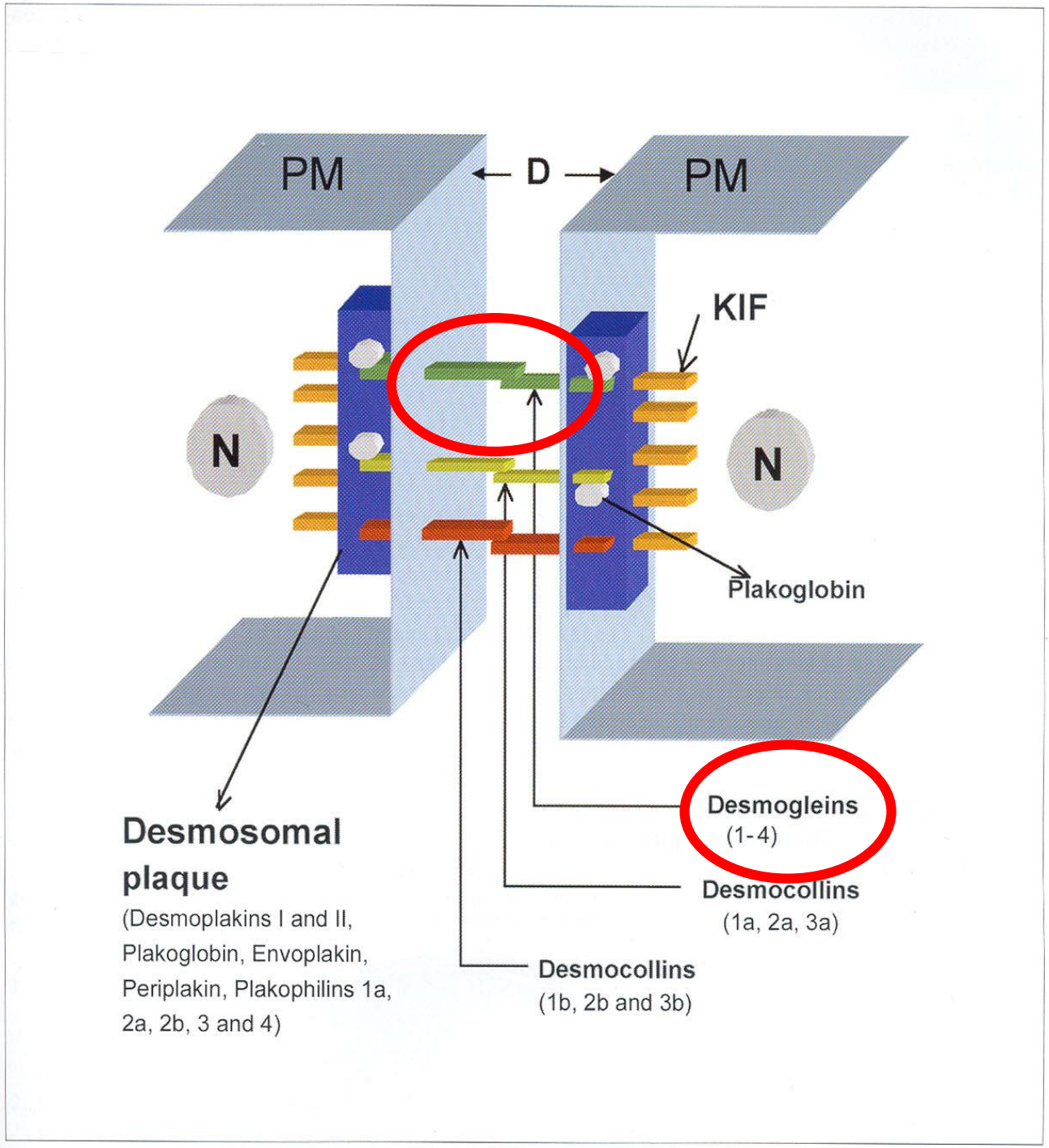
Dermatitis herpetiformis
Linear Ig A bullous dermatosis
Epidermolysis bullosa acquisita

subepidermal blister formation

Pemphigus

Pemphigus. Epidemiology

- the incidence of pemphigus in Europe is 0.5-8/1 000 000/year.
- it is slightly more common in women
- peak incidence: 50-60 y
- in most countries, pemphigus vulgaris is the most common type of pemphigus


PM
D
PM
KIF
N
N
Plakoglobin
Desmosomal plaque
(Desmoplakins I and II, Plakoglobin, Envoplakin, Periplakin, Plakophilins 1a, 2a, 2b, 3 and 4)
Desmogleins (1-4)
Desmocollins (1a, 2a, 3a)
Desmocollins (1b, 2b and 3b)

Pemphigus. Etiopathogenesis

- production of autoantibodies against desmosomal cadherins (cell adhesion molecules)- desmogleins
- binding of antibodies to desmogleins causes acantholysis- disruption of connections between cells (loss of cell-cell adhesion)
- sometimes the association of the disease with specific HLA (e.g. in pemphigus vulgaris HLA-DRB1*0402 in Ashkenazi Jews or HLA-DRB1*04 and HLA-DRB1*14 in non-endemic pemphigus foliaceus)

Pemphigus. Exogenous factors

- drugs (containig thiol group -SH and non- thiol drugs): penicillamine , ACE inhibitors (eg. captopril), angiotensin receptor blockers, penicillins , cephalosporins , NSAIDs, calcium channel inhibitors
- vegetables - Allium group containing SH group (onion , leek ,garlic)
- thermal burns
- mechanical trauma
- UV
- viral infections

Food- induced pemphigus

vegetables - Allium groups

garlic , leek , onion

blisters and erosions

chemical acantholysis

SH and S=S groups

Pemphigus vulgaris

Pemphigus vulgaris

pemphigus vulgaris is a potentially life-threatening disease:

- **disruption of the epidermal barrier leading to fluid loss**
- **risk of secondary bacterial infections**

Pemphigus vulgaris

- mucosal dominant type (no or limited cutaneous involvement)
- mucocutaneous type

Pemphigus vulgaris. Mucous membranes

70-90% of patients - the first location is oral mucosa (erosions that occur after blisters that rupture quickly)- mucosal phase

- typically mucosa of the cheeks, soft palate, tongue,sometimes desquamative gingivitis
- lips- erosions are covered with crusts, sometimes hemorrhagic.
- other mucosal locations: nasal cavity, pharynx, larynx, trachea, esophagus, conjunctiva, genital mucosa, anus

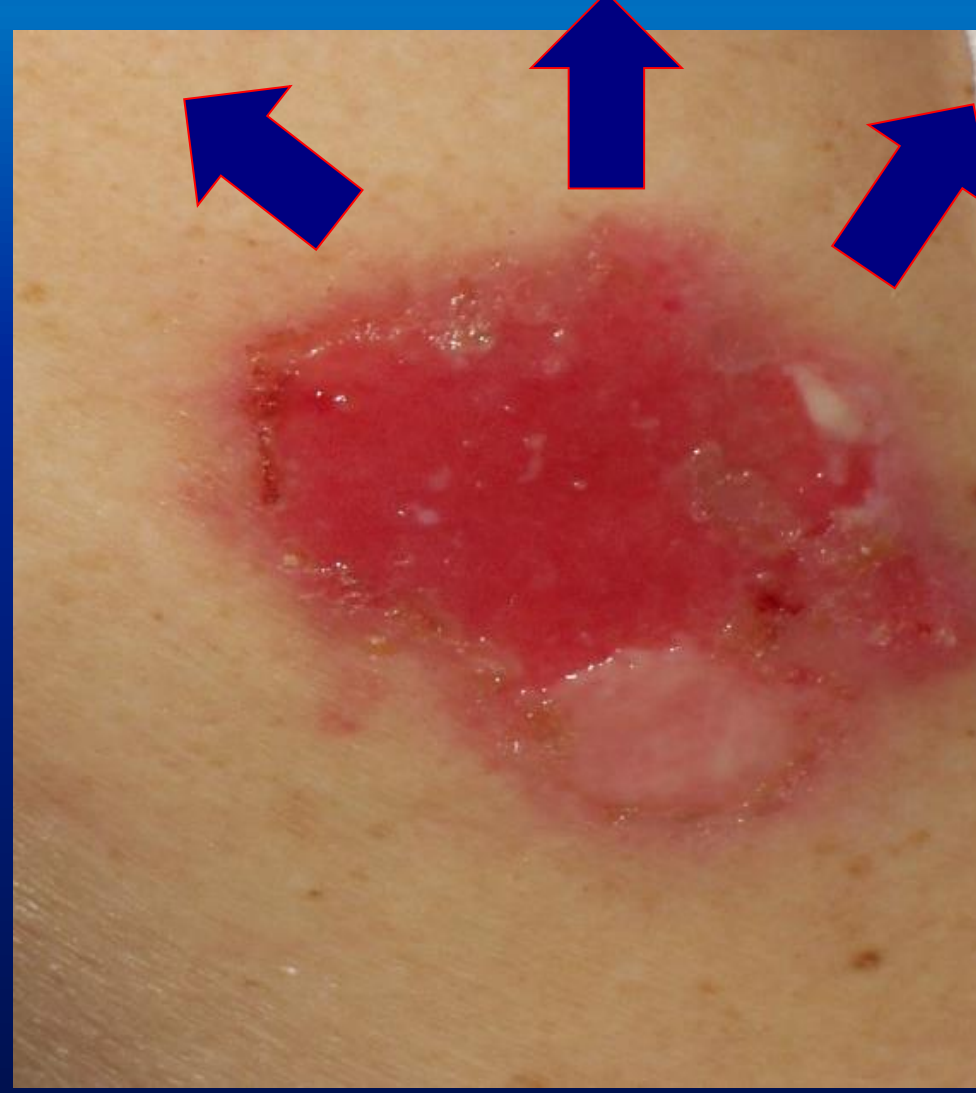
Pemphigus vulgaris

- several weeks or months after the onset of the first mucosal symptoms most patients develop blisters on glabrous and/or hairy skin (mucocutaneous phase)
- typically the skin of the face, trunk, scalp
- Nikolsky's sign I and II (Nikolsky's and Asboe –Hansen's)

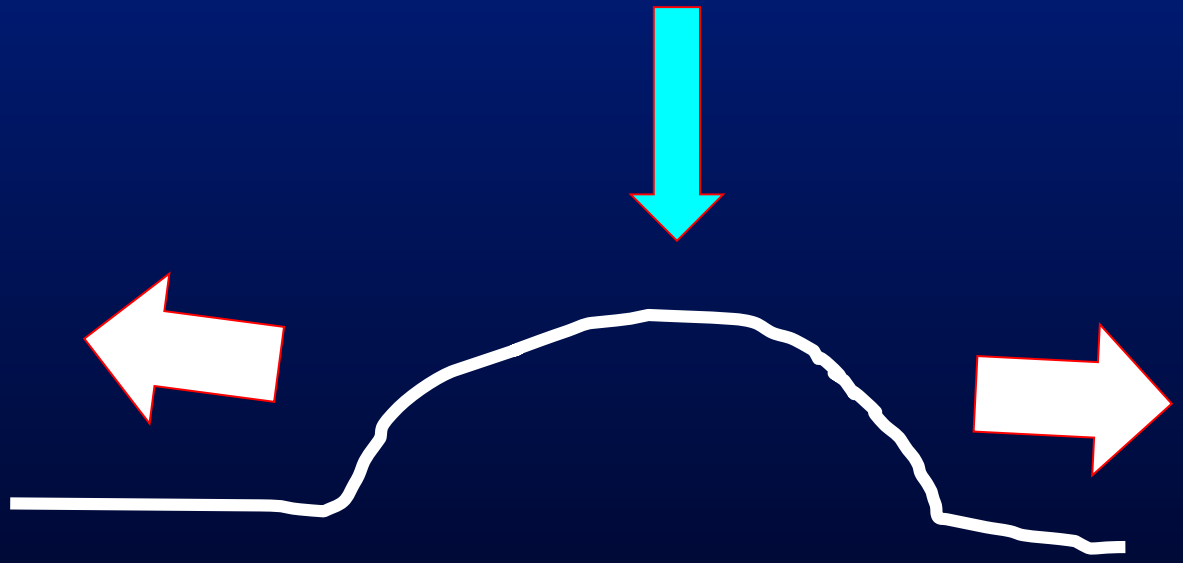
Nikolsky's sign I- is a condition in which the superficial layers of skin detach from lower layers with a slight rubbing

Nikolsky's sign II (Asboe-Hansens's sign)- extension of a blister to adjacent skin when pressure is put on the top of the blister

Nikolsky’s sign I



Nikolsky’s sign II (Asboe – Hansen’s sign)



Pemphigus vegetans

- variant of pemphigus vulgaris
- Types: bullous (Neumann) and pustular (Hallopeau)
- location: intertriginous area (skin folds), genital area, nasolabial folds
- erosions and verrucous hypertrophic lesions

Pemphigus foliaceus

Pemphigus foliaceus

- flaccid blisters, easily ruptured
- superficial erosions
- scaling and crusts
- often erythematous lesions
- disease is localized or generalized
- sometimes erythroderma

there are no mucosal changes in the course of pemphigus foliaceus

Pemphigus erythematosus

- localization: seborrheic areas (scalp, face, sternum area, interscapular area)
- erosions, erythematous lesions and scaling
- lesions resembling lupus erythematosus and seborrheic dermatitis

Pemphigus erythematosus

- in some patients, the coexistence of immunologic features of pemphigus with immunologic features of lupus erythematosus (circulating and in vivo bound antinuclear antibodies).
- the overlapping features of both diseases - Senear-Usher syndrome

Pemphigus herpetiformis

- small vesicles in annular or herpetiform arrangement, localized on urticarial , erythematous plaques
- skin itching

about 80% of cases – variant of pemphigus foliaceus
about 20% of cases – variant of pemphigus vulgaris

Paraneoplastic pemphigus

Paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome, PAMS)

- about 2/3 cases – lymphomas, non-Hodgkin 's disease and chronic lymphocytic leukemia
- Castleman's disease (typically in children)
- adenocarcinomas (e.g. prostate, pancreas, breast cancer)
- thymomas
- sarcomas
- Waldenstrom's macroglobulinemia .

in most cases, the diagnosis of malignancy is made before symptoms of paraneoplastic pemphigus develop .

Paraneoplastic pemphigus

initial symptom: dominant mucosal involvement: severe stomatitis

- extensive erosions
- deep, necrotic ulcers
- lateral surfaces of the tongue, haemorrhagic crusts on the lips

other mucous membranes:
conjunctivitis (pseudomembranous inflammation can lead to scarring in some cases), the mucous membrane of the nose, throat, esophagus, genital area, anus.

Paraneoplastic pemphigus

- skin changes resemble pemphigus vulgaris, bullous pemphigoid, erythema multiforme, lichen planus, GVHD
- characteristic involvement of the hands and feet

Paraneoplastic pemphigus
(paraneoplastic autoimmune multiorgan syndrome)

- internal organ involvement
- development of bronchiolitis obliterans

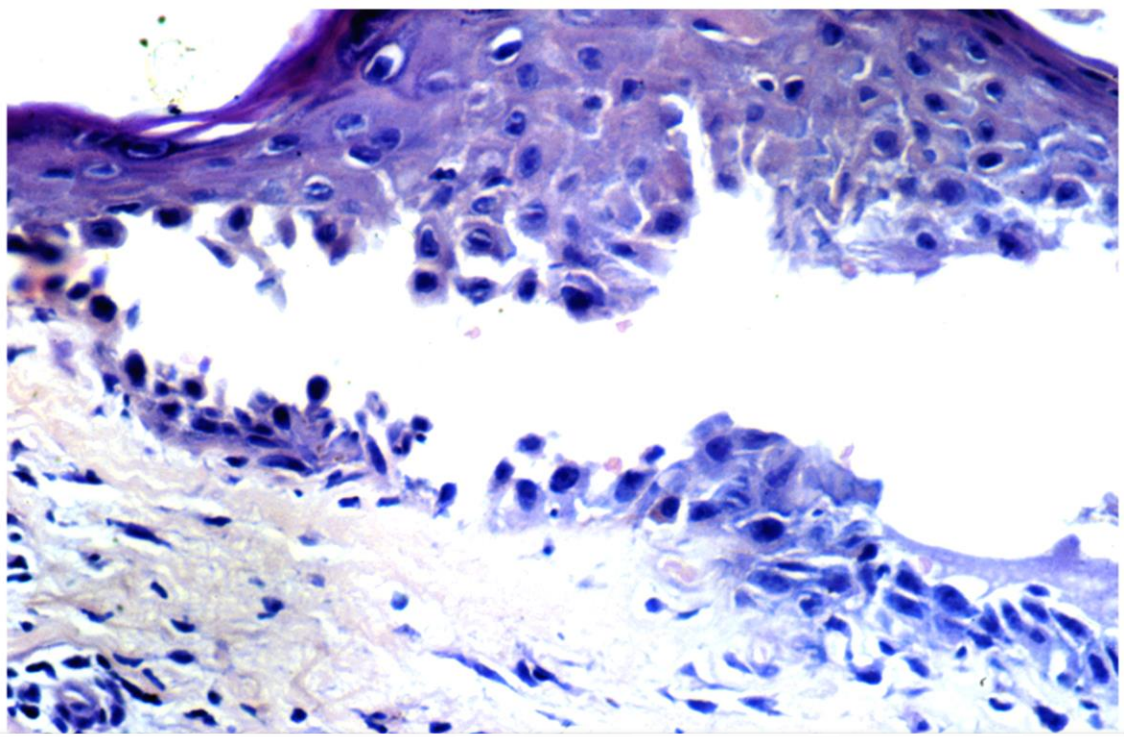
  - high risk of death

Pemphigus. Diagnosis

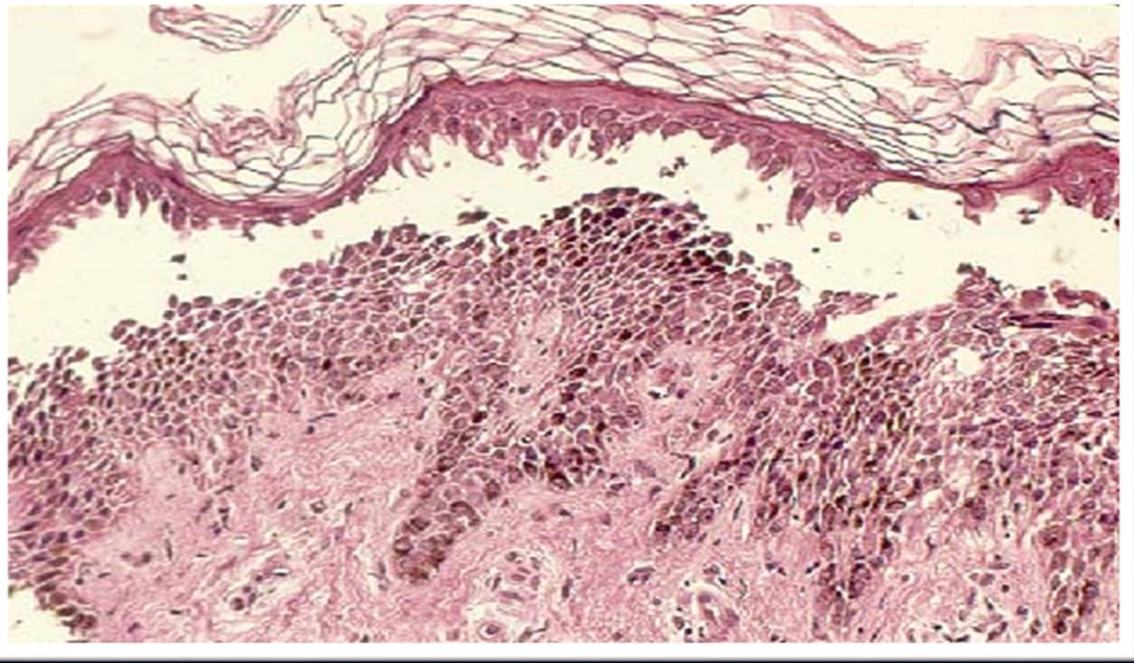
Pemphigus. Histopathology

intraepidermal blisters resulting from acantholysis (loss of intercellular connection as a result of antigen-antibody reaction)

pemphigus vulgaris - acantholysis just above the basal layer (deep)
pemphigus foliaceus - acantholysis under the stratum corneum (superficial)



Pemphigus vulgaris (deep or suprabasilar acantholysis)



Pemphigus foliaceus (superficial acantholysis)

intraepidermal blister formation due to a loss of cell–cell adhesion of keratinocytes-acantholysis

Pemphigus. Diagnostic tests. Direct immunoflorescenece test.DIF

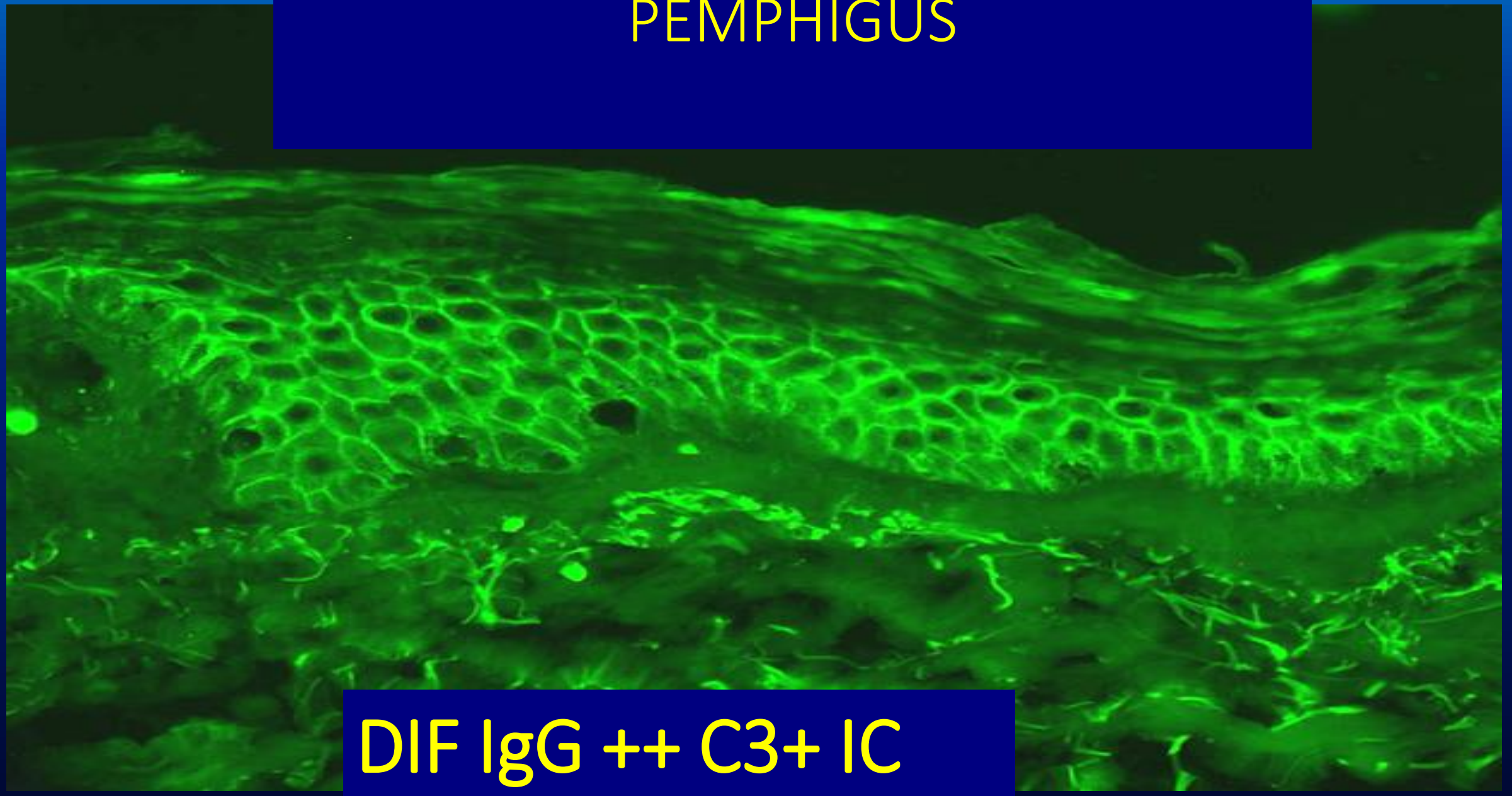
basis for the diagnosis

direct immunofluorescence DIF

substrate: perilesional skin, a few millimiters to 1 cm from the lesion

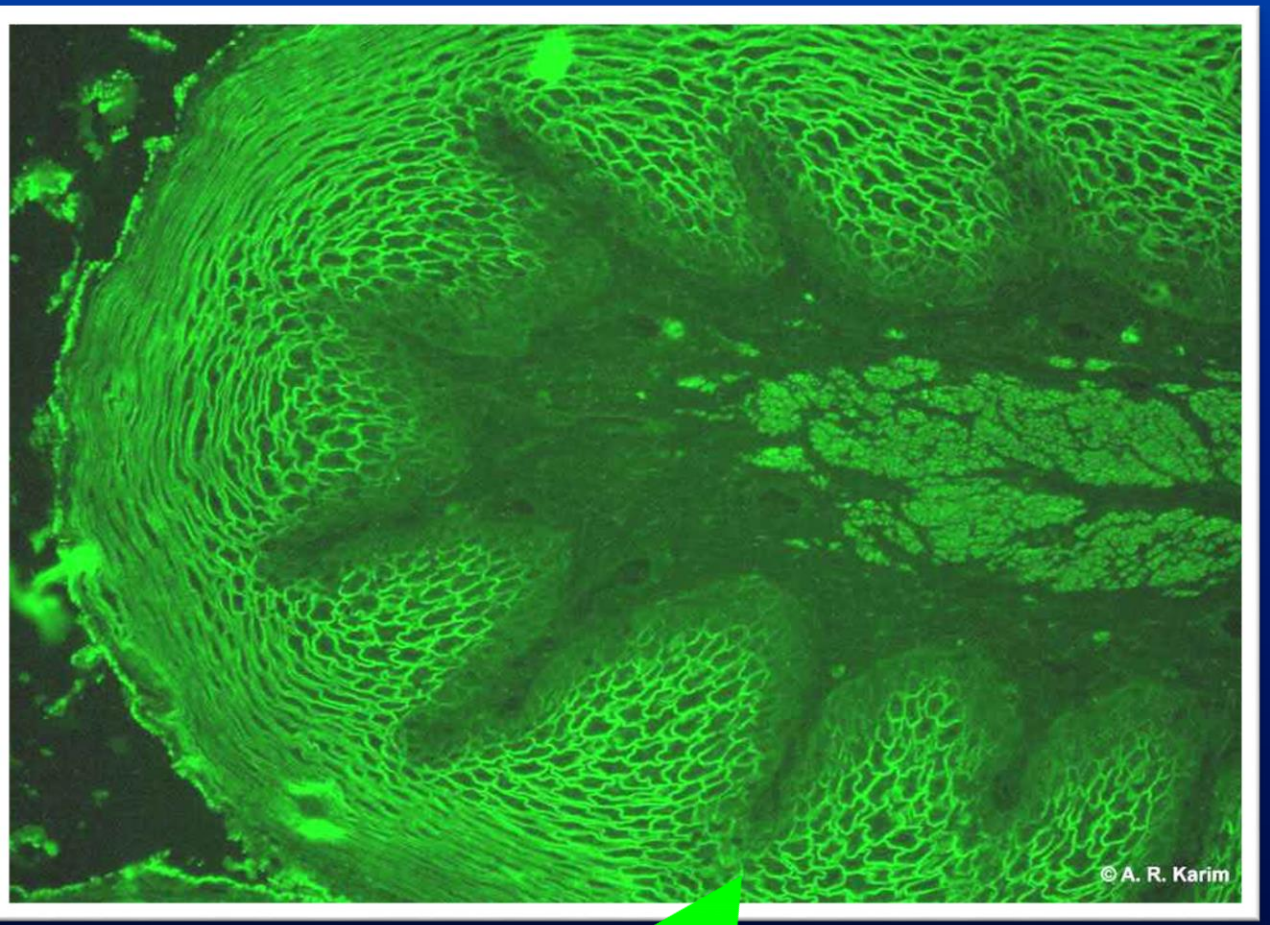
DIF IgG + C3+ intercellular deposits in the epidermis („honeycomb pattern, fish net pattern")

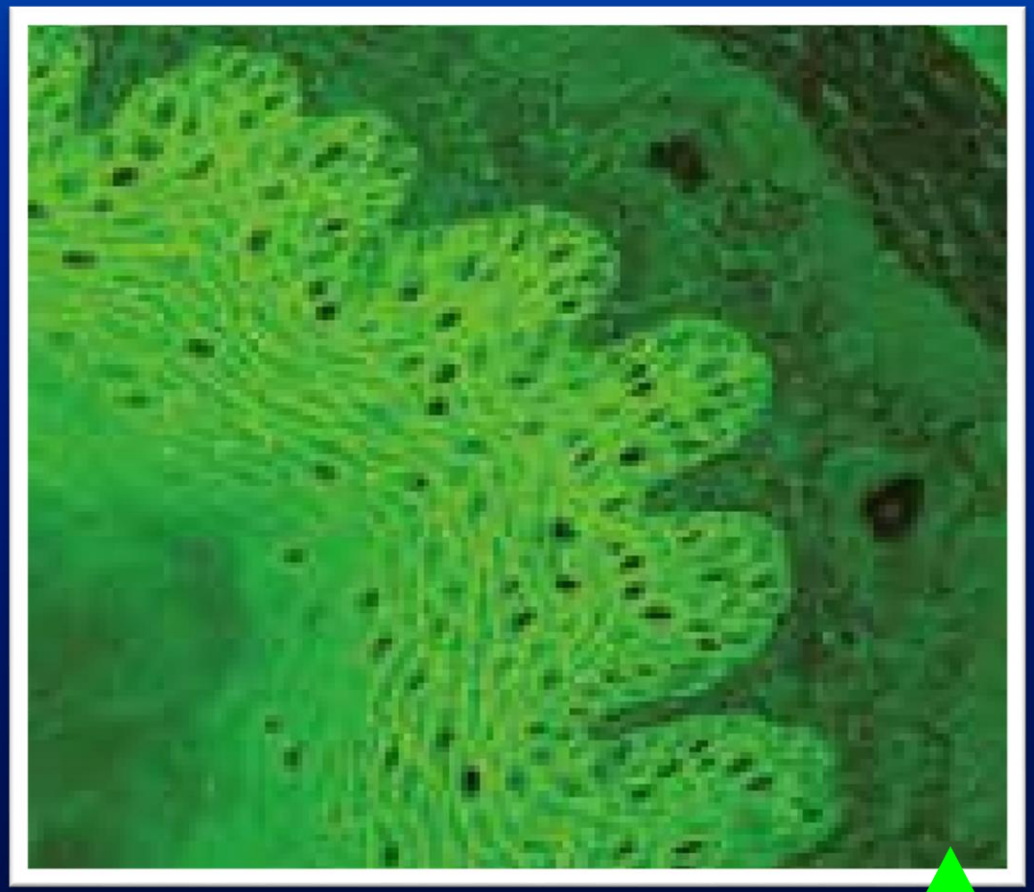
PEMPHIGUS



DIF IgG ++ C3+ IC

Indirect immunofluorescence test. IIF



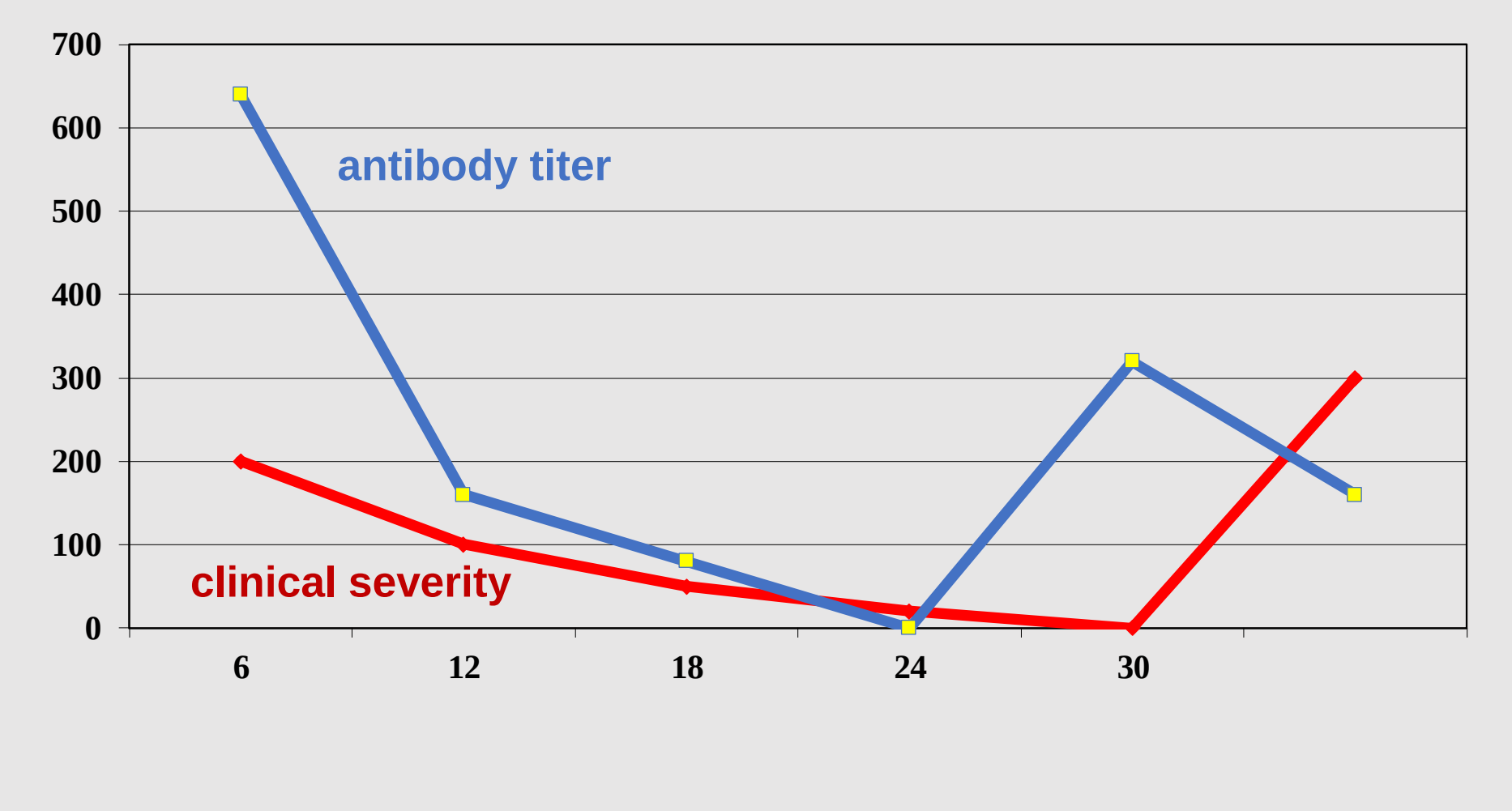


monkey esophagus

IIF ME 160 IgG IC
GPE 20 IgG IC

guinea pig esophagus

Correlation of clinical picture and antibody titer



Pemphigus. Indirect immunofluorescenece test (IIF)

- pemphigus vulgaris- higher titers on the monkey esophagus as a substrate than on the guinea pig esophagus
- pemphigus foliaceus- higher titers on guinea pig esophagus or equal titers on both substrates (monkey esophagus and guinea pig esophagus)
- paraneoplastic pemphigus- substrate: rodent urinary bladder (e.g. rat bladder) or lung,

Pemphigus. ELISA

- the most sensitive and specific method to detect pemphigus antibodies
- antibodies against desmoglein 1 and 3 (anti Dsg 1 and 3)

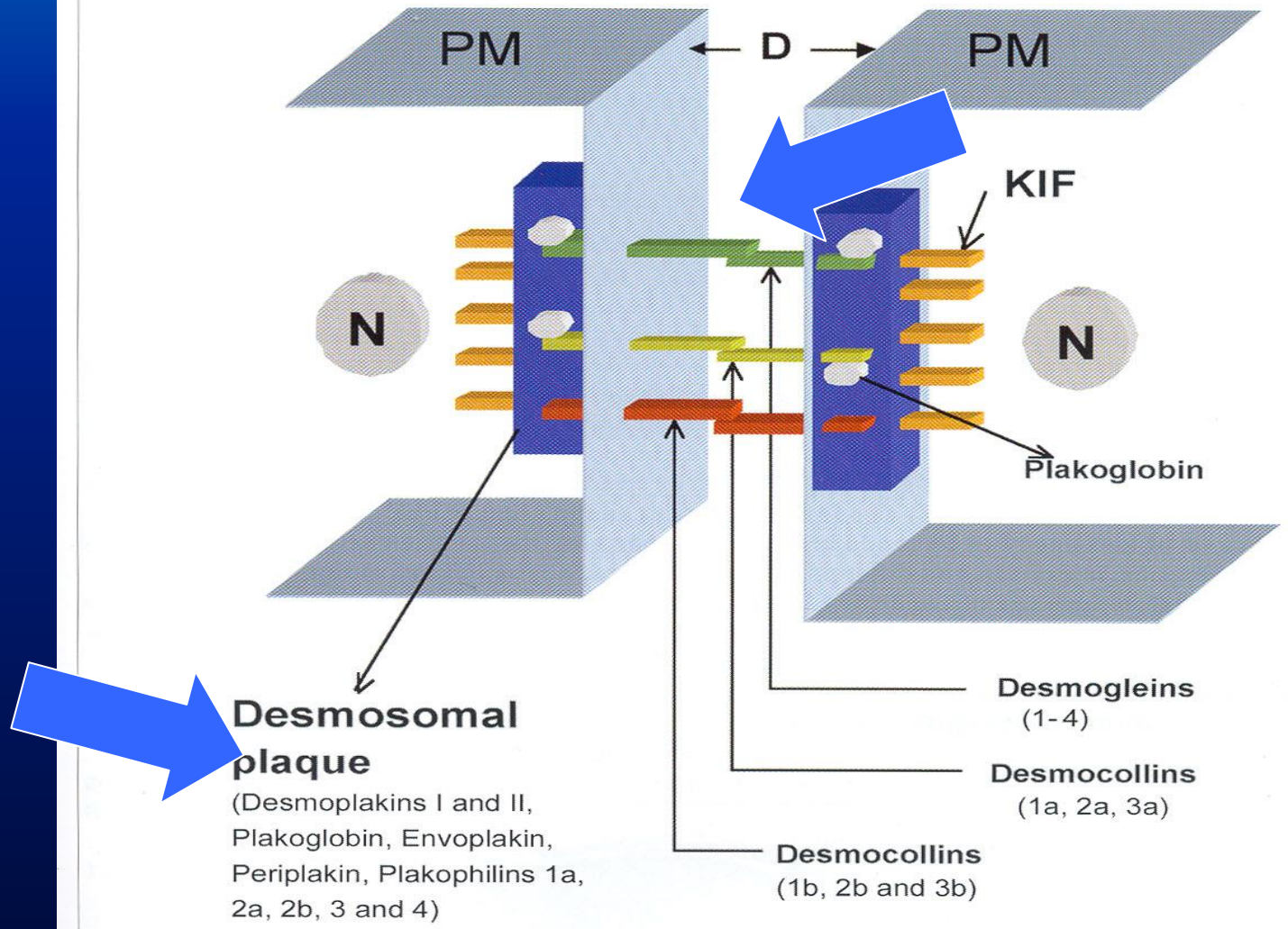
ELISA index

PV mucosal form	anti Dsg 3
PV mucocutaneous form	anti Dsg 1 and Dsg 3
PF	anti Dsg 1

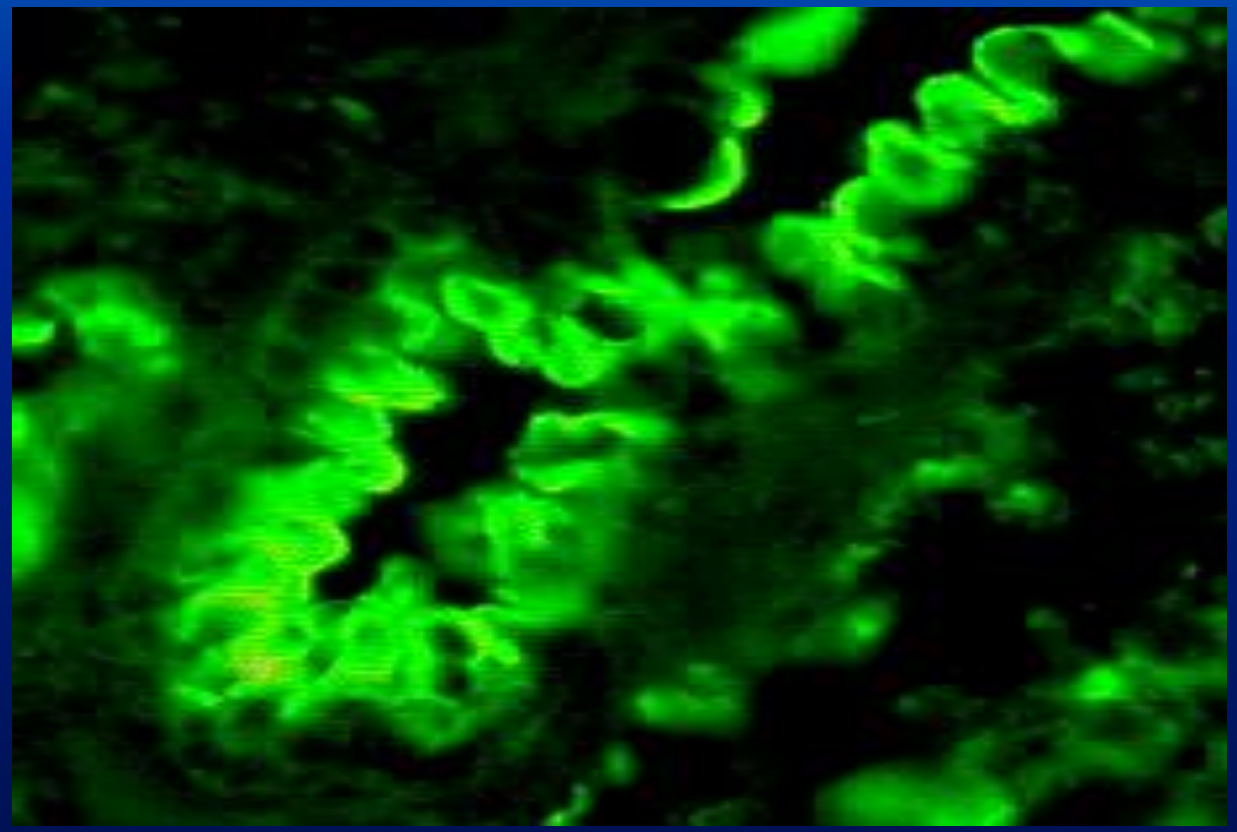
Paraneoplastic pemphigus (pemphigus paraneoplasticus , paraneoplastic pemphigus , PAMS)

Plakin family antibodies :
envoplakin , periplakin, epiplakin, plectin,
desmoplakin I, desmoplakin II

BPAG1, A2ML1 protein (α2-macroglobulin-like protein 1) desmogleins and desmocollins

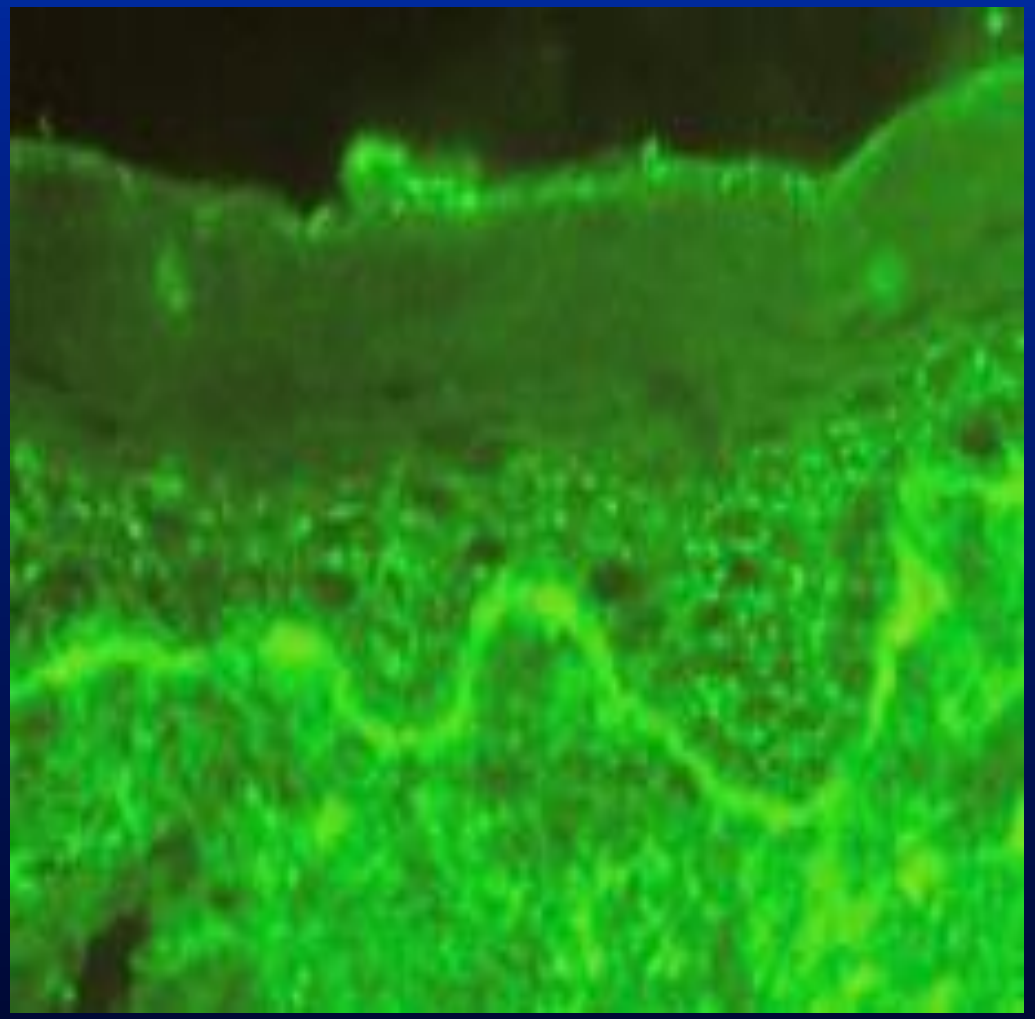

PM
D
PM
KIF
N
N
Plakoglobin
Desmogleins
(1-4)
Desmocollins
(1a, 2a, 3a)
Desmocollins
(1b, 2b and 3b)
Desmosomal plaque
(Desmoplakins I and II, Plakoglobin, Envoplakin, Periplakin, Plakophilins 1a, 2a, 2b, 3 and 4)

Paraneoplastic pemphigus. IIF



pemphigus antibodies detected on the rat lung substrate

Paraneoplastic pemphigus.
DIF (direct immunofluorescence)



DIF IgG, C3 IC
IgG, C3 BMZ

Zimmermann, 2009

Pemphigus. Treatment

Rituximab (RTX) (anti-CD20)

- **drug of first choice of pempigus treatment, especially in patients with newly diagnosed pemphigus (moderate to severe cases), and in individuals who have not achieved remission with another method of treatment.**
- **in monotherapy or in combination with glucocorticosteroids , most commonly:**
  RTX 2x 1000 mg *iv* at an interval of 14 days
- **in case of relapse, re-use of rituximab is possible .**

Pemphigus. Treatment

- **the classic drugs are glucocorticosteroids: prednisone or prednisolone orally (1.0-1.5 mg/kg / day) lower doses - mucosal pemphigus vulgaris and in some cases of pemphigus foliaceus**
- **glucocorticoids are usually combined with immunosuppressants: eg.azathioprine (1–3 mg/kg/d, mycophenolate mofetil).**

Pemphigus. Treatment

combined therapy

prednisone (prednisolone)
1.0-1.5 mg/kg/d

azathioprine 1-3 mg/kg/d

Pemphigus. Treatment

other drugs added to glucocorticoids

- mycophenolate mofetil
- cyclophosphamide
- dapsone (herpetiform pemphigus)

or

- glucocorticosteroids iv
- IVIG
- immunoadsorption

Bullous pemphigoid

Bullous pemphigoid (pemphigoid bullous)

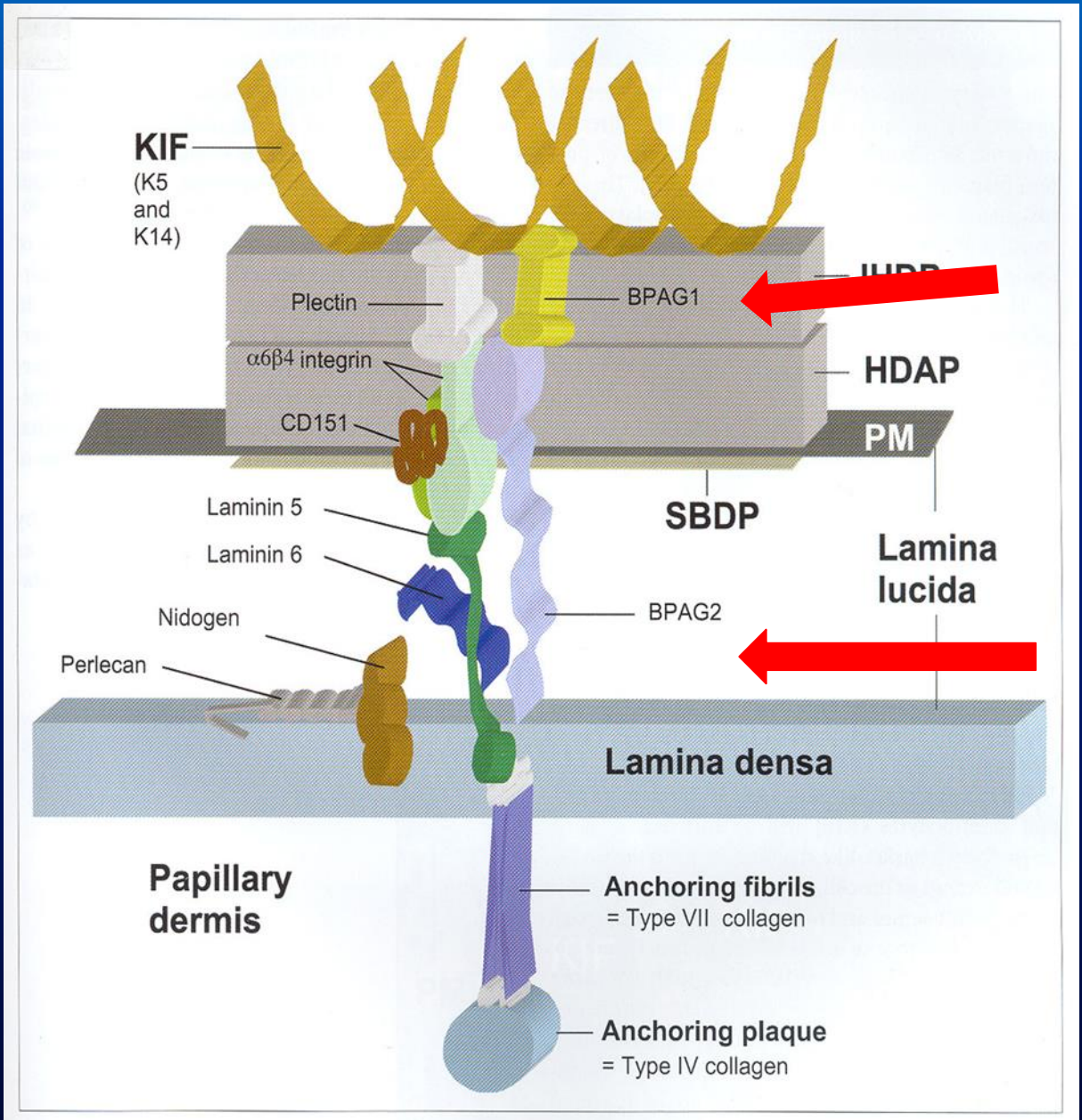
the most common autoimmune blistering disease

- 0.2 - 4 cases/100 000/year
- age >70
- increase in incidence with age
- M>F

Pemphigoid

coexistence with:

- diseases of the cardiovascular system,
- neurological and psychiatric diseases (strokes, dementia, Parkinson's disease, epilepsy, schizophrenia, bipolar disorder)
- diabetes



230 kD (BPAG1)

180 kD (BPAG2)

Pemphigoid. Etiopathogenesis

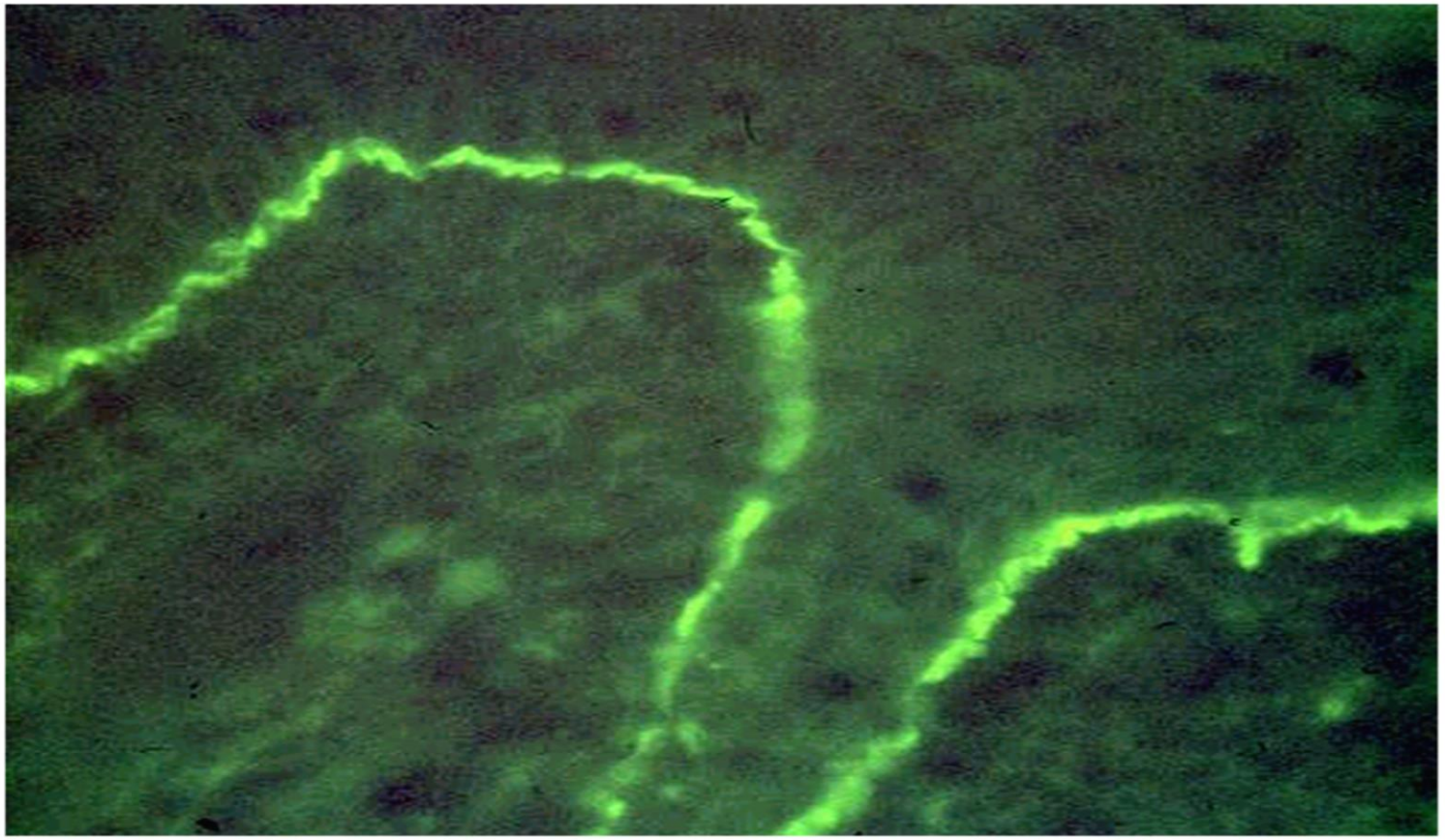
- drugs (e.g. spironolactone , furosemide , and DPP-4 inhibitors [gliptins] ,and PD-1 and PD-L1 inhibitors, penicillins, ciprofloxacin , sulfonamides, ACE inhibitors, neuroleptics)
- UV (PUVA)
- mechanical and thermal injuries
- viral infections

Pemphigoid. Clinical picture

- **prodromal phase: papules, urticaria-like changes, erythematous changes**
- **subepidermal , tense blisters (sometimes hemorrhagic) located on healthy skin and on the erythematous base**
- **typical location: flexural surface of limbs, trunk**
- **skin itching**
- **20-30% - involvement of mucous membranes**
- **there are cases without bullous eruptions**

Pemphigoid. Variants

- dyshydrotic
- vesicular
- localized
- seborrheic
- vegetans
- erythroderma
- anti - p200 pemphigoid (anti- laminin γ 1) younger patients, hand and feet involvement, erythematous lesions and blisters, pruritus, mucosal involvement in 20%, coexistence with psoriasis (approx. 30%)

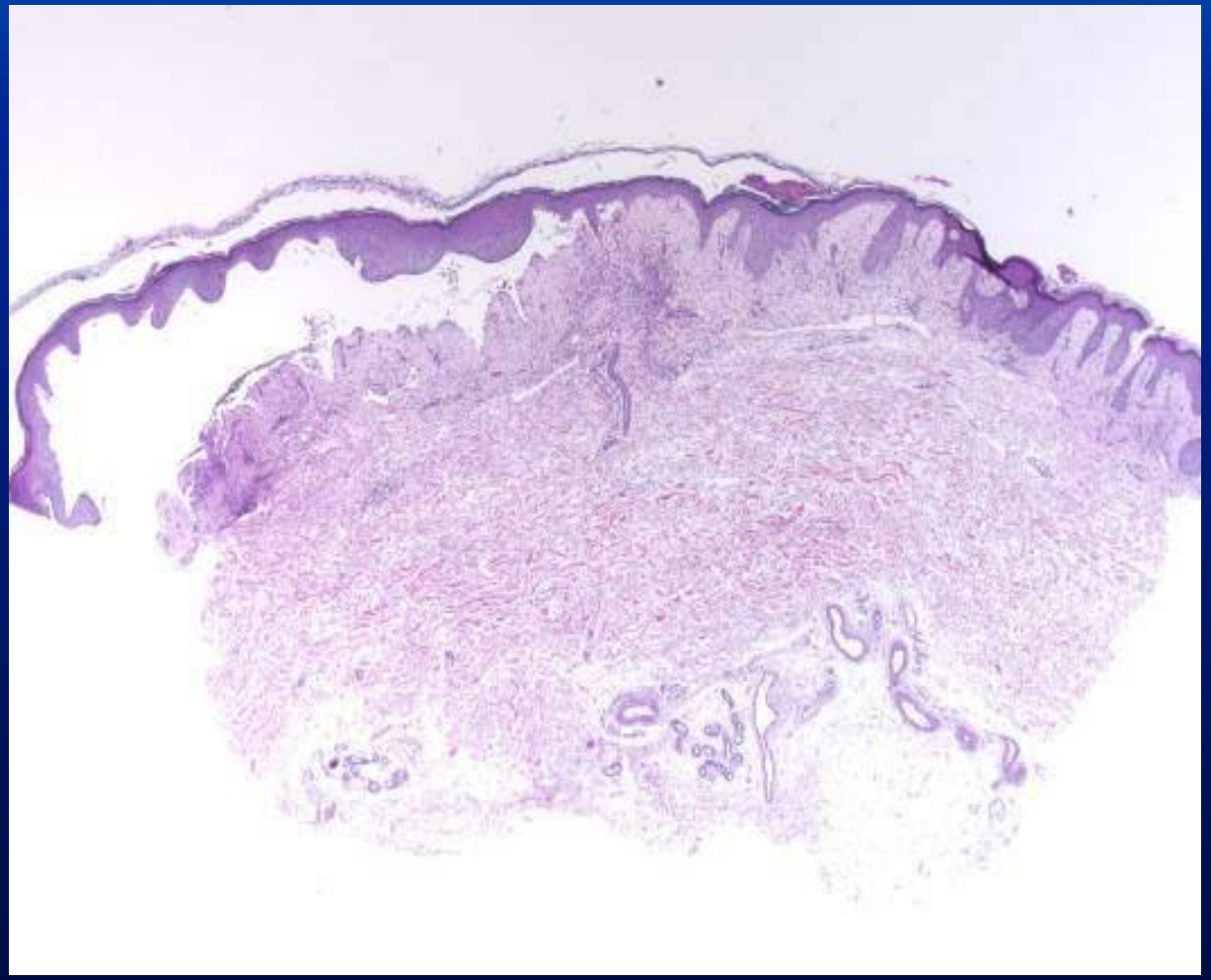


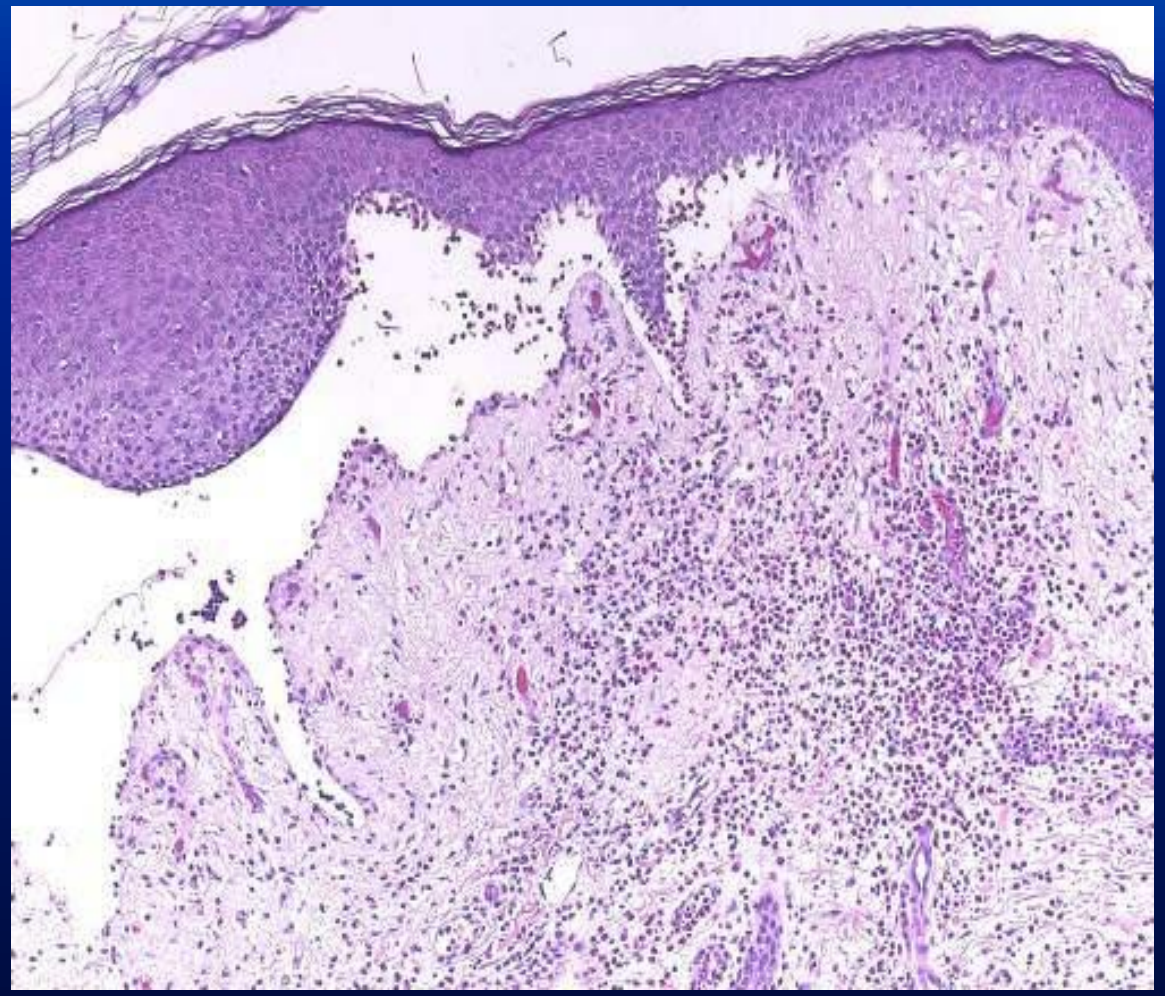
IgG and C3 bound in the membrane zone zone

DIF IgG and C3 BMZ

IIF IgG BMZ (65-80%)

ELISA 180 kD (NC 16A) and 230 kD





Pemphigoid. Diagnosis

- DIF - IgG + C3 + along the basement membrane (linear staining)
- IIF - IgG antibodies in the basement membrane zone
- ELISA – antibodies against NC16a 180 kD (correlation with disease activity)
- histopathology - subepidermal blisters

Pemphigoid. Topical treatment

propionate clobetasol
30 - 40 g/ d (severe cases)
20 - 30 g/day (moderate cases)
whole skin surface (including blisters and erosions), not on the face

- every day - first month
- every 2 days - second month
- 2 times a week - third month
- 1x a week - fourth month
- in some cases maitenance therapy 10 g / 7 days - 8 months

Pemphigoid. Systemic treatment

- glucocorticoids : prednisone - 0.5-0.75 mg/kg and tapering the dose
- methotrexate : 7.5-15 mg/ 7 days
- doxycycline
- other: azathioprine , mycophenolate mofetil , dapsone, cyclophosphamide , rituximab , omalizumab (pemphigoid IgE), dupilumab

Internal malignancy screening, but bullous pemphigoid is not regarded as a paraneoplastic disease

Mucous membrane pemphigoid

Mucous membrane pemphigoid.
Localization

- oral mucosa (approx. 75-85%)
- conjunctiva (approx. 65%)
- nose
- throat
- larynx
- trachea
- esophagus
- genital mucosa
- skin (approx. 25%)

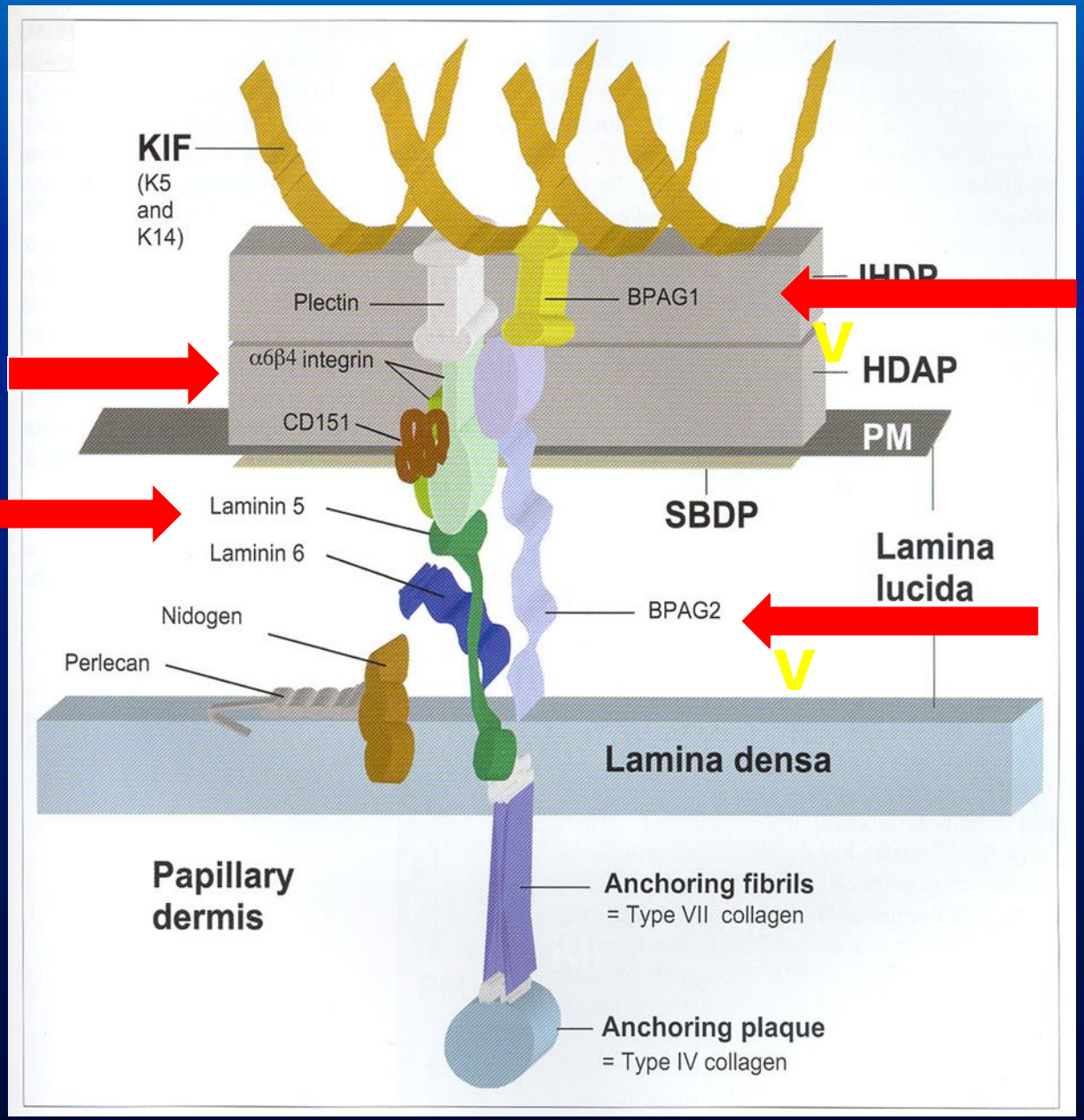
Mucous membrane pemphigoid. Oral mucosa

the most frequently involved location

erythema, blisters (hemorrhagic)
desquamative gingivitis
palate (cheeks, tongue, lips)

Mucous membrane pemphigoid

- DIF- linear IgG (+ IgA) + C3 deposits along BMZ (basement membrane zone)
- antibodies against 180 kD, 230 kD , laminin 332 (epiligrin), α6 β4-integrin


KIF
(K5
and
K14)
Plectin
BPAG1
α6β4 integrin
HDAP
CD151
PM
SBDP
Laminin 5
Laminin 6
Lamina
lucida
BPAG2
Nidogen
Perlecan
Lamina densa
Papillary
dermis
Anchoring fibrils
= Type VII collagen
Anchoring plaque
= Type IV collagen

Mucous membrane pemphigoid.
Specific variants

Brunsting - Perry

typically in older men
blisters on the scalp
the lesions resolve with scarring

Pemphigoid with anti -laminin 332 (epiligrin) antibodies

association with internal malignancy

Pemphigoid gestationis

Pemphigoid gestationis

- II, III trimester of pregnancy, relapses in subsequent pregnancies
- 1:50 000-60 000 pregnancies
- HLA-DR3 and HLA-DR4
- antibodies cross-react with the basement membrane of the epidermis and the placental epithelium
- rarely after preganancy and in connection with hormonal drugs
- association with autoimmune thyroid diseases
- descriptions of the occurrence of hydatidiform mole and choriocarcinoma

Pemphigoid gestationis. Clinical picture

- prodromal stage – erythematous, urticarial , papular lesions
- followed by tense blisters
- typical localization - the skin of the abdomen, arround the umbilicus
- involvement of mucous membranes - 20%
- itching, burning

Pemphigoid gestationis

- passive transfer of antibodies from mother to child (5-10% of cases)
- sometimes premature birth or low birth weight
- rarely development of skin lesions in child

Pemphigoid gestationis. Diagnosis

- DIF - linear deposits of C3, sometimes IgG along the basement membrane

in some patients:

- IIF - IgG antibodies against BMZ
- ELISA - antibodies against 180kD (rarely 230kD)

Pemphigoid gestationis. Treatment

- topical- glucocorticosteroids
- systemic- glucocorticoids , antihistamines
- the disease may be self-limiting

Dermatitis herpetiformis

Duhring's disease

Dermatitis herpetiformis. Clinical picture

- polymorphic skin lesions: vesicules, papules, erythematous changes, urticaria-like changes, sometimes large blisters, secondary excoriations and hyperpigmentation
- rare mucosal involvement (aphthosis)
- remissions and exacerbations, spontaneous remissions

itching and burning

Dermatitis herpetiformis. Clinical picture

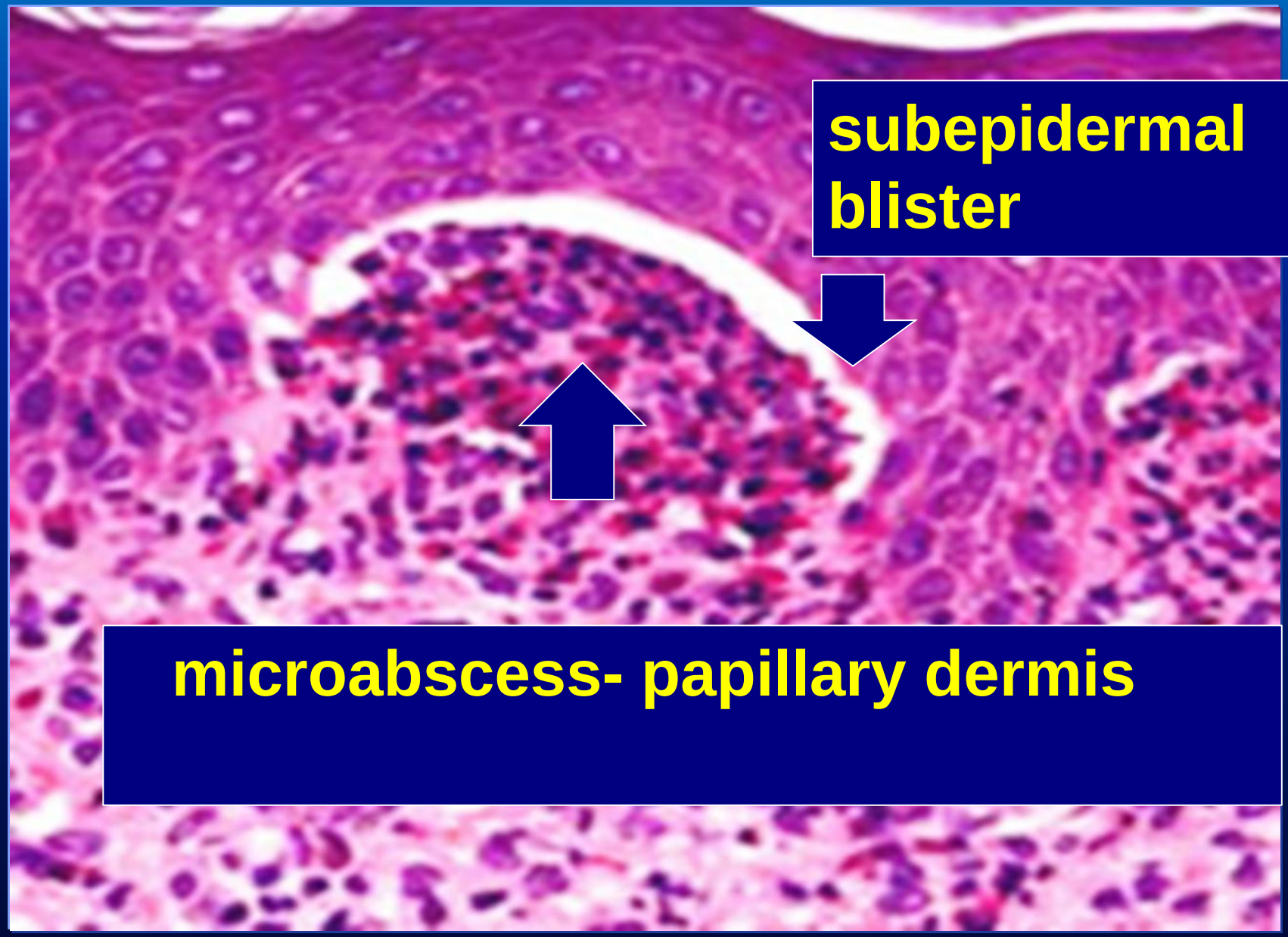
symmetrically located skin lesions:

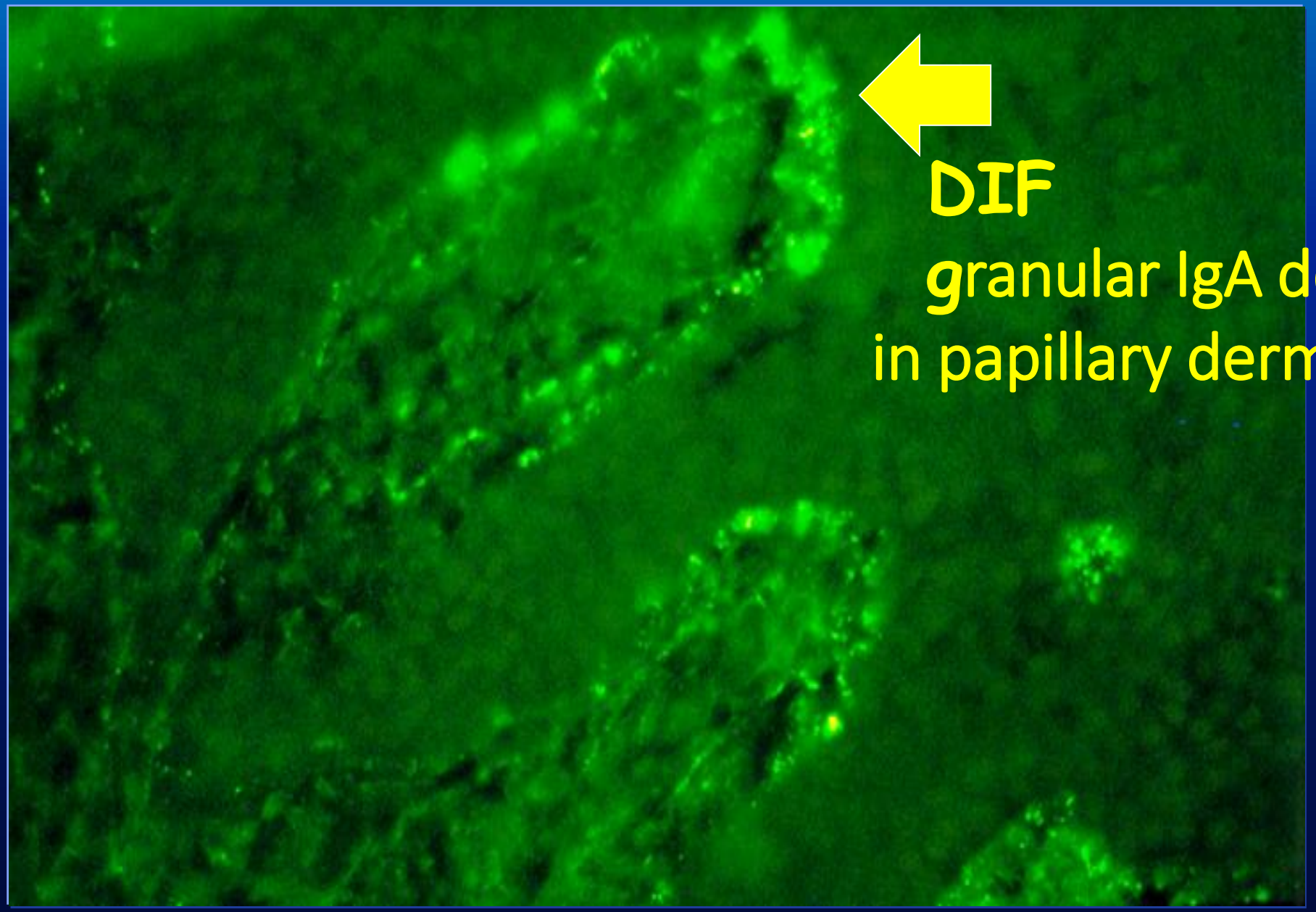
- extensor surfaces:
  elbows, knees (90%)
- sacro-lumbar region, buttocks, shoulder blades, shoulder girdle,
- scalp, face

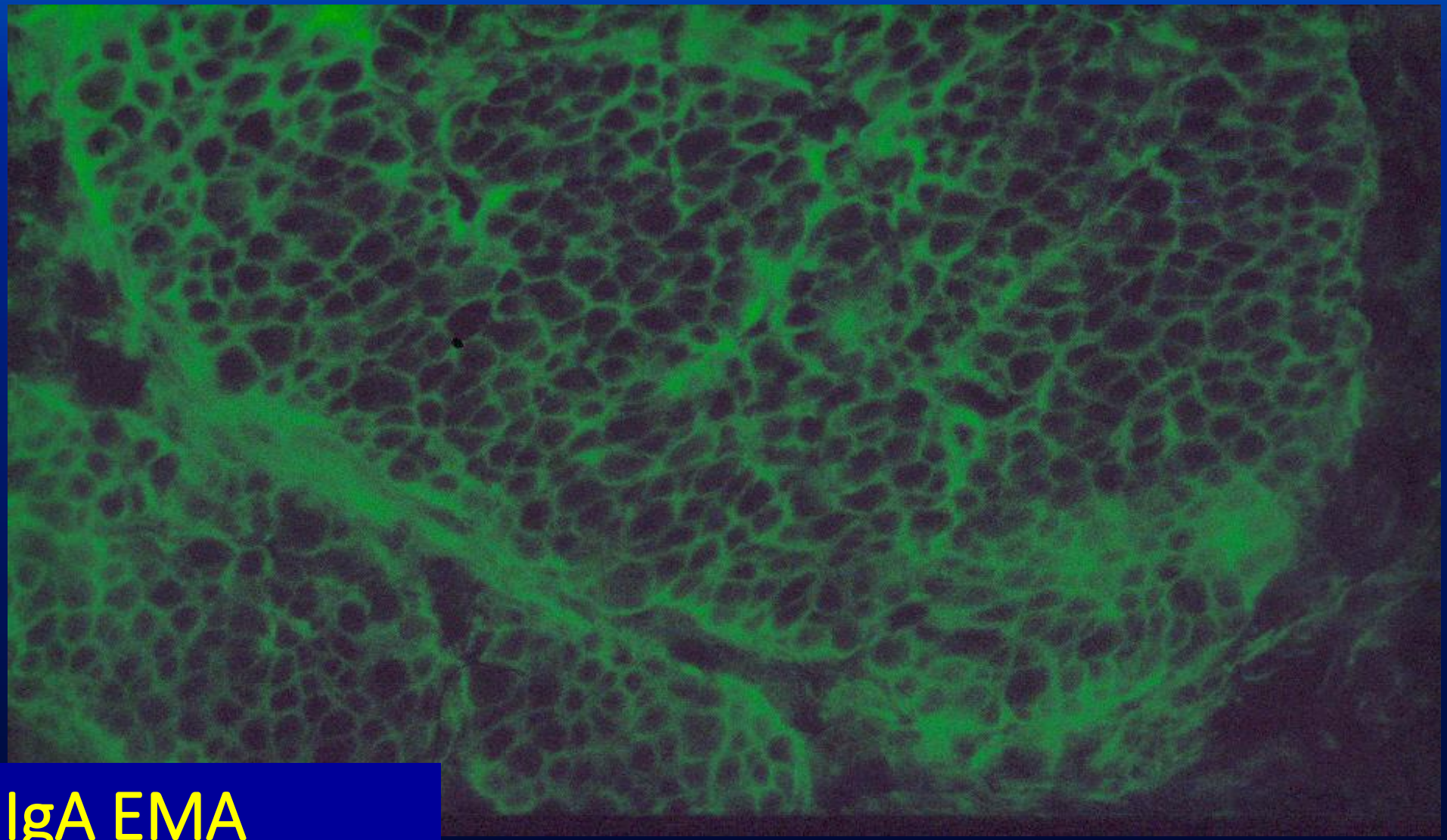
Dermatitis herpetiformis

- 1.2–75.3/100,000
- HLA-DQ 2, 8
- M>F
- age 40-50
- especially northern Europe
- gluten-dependent enteropathy (90%)
- exacerbation of skin lesions after gluten and iodine
- increased risk of developing B-cell lymphoma
- coexistence with other autoimmune diseases

(thyroid diseases , vitiligo, diabetes)


subepidermal blister
microabscess- papillary dermis


DIF
granular IgA depositis
in papillary dermis



IIF: IgA EMA

Dermatitis herpetiformis. Diagnosis

- DIF (**normal appearing perilesional skin**) - granular IgA deposits- dermal papillae
- IIF IgA EMA (antiendomysial antibodies)
- ELISA antibodies against tissue transglutaminase
- Histopathology- **neutrophilic microabscesses within dermal papillae,** subepidermal blisters

Dermatitis herpetiformis. Treatment

1.gluten-free diet - has a therapeutic effect on skin and intestinal changes, improvement after a few months of use

2.sulfones (dapsone) - has a herapeutic effect only on skin changes, quick improvement (1-2 days)
50 mg ⟵ 100 mg, then attempts to lower

3. iodine avoidance , including low-iodine diet

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD)

- children 4-5 years of age (the most common autoimmune bullous disease in children)
- adults 60-65 years old
- association with HLAB8, DR3, DQ2, Cw7
- induction by drugs (vancomycin, sometimes non-steroidal anti-inflammatory drugs, ACE-inhibitors , cephalosporins)
- adults - neoplastic diseases- lymphoproliferative disorders, cancers

Linear IgA bullous dermatosis

- clinical features of bullous pemphigoid and dermatitis herpetiformis
- blisters, vesicles (sometimes hemorrhagic) with an annular arrangement,"strings of pearls" erythematous and urticarial lesions

Linear IgA bullous dermatosis

- about 50% of patients (more often in children than in adults) - mucosal changes, mainly oral mucosa
- possible involvement of the pharynx, larynx , trachea and conjunctivitis with scarring
- characteristic localization in children abdomen, groins, genital area, armpits, face
- skin itching

Linear IgA bullous dermatosis
Diagnosis

- DIF- IgA deposits along the basement membrane
- IIF-antibodies against the 180 kD antigen (120, 97 kD) - 30-50% of cases

Linear IgA bullous dermatosis
Treatment

- dapsone
- dapsone and glucocorticoids
- less frequently other immunosuppressants: mycophenolate mofetil , IVIG

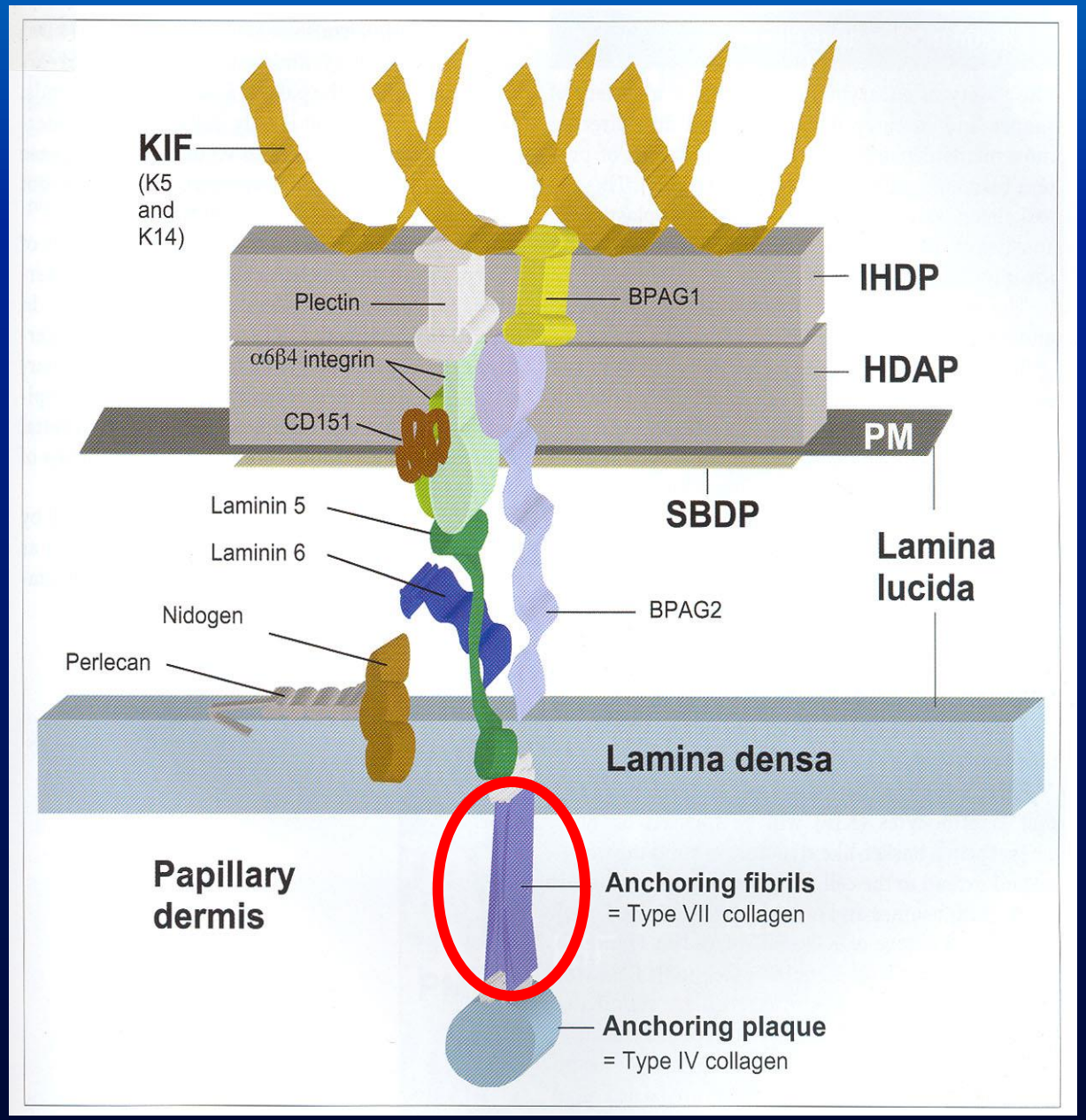
Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA)

- blisters (sometimes hemorrhagic) in places of mechanical injuries, extensor surfaces of the limbs (hands, feet, elbows, knees)
- they regress with scars, milia
- involvement of the mucous membranes
- in the inflammatory form, rapid course, erythematous changes, urticaria-like (similar to BP and LABD)
- scarring within the mucous membranes (oral mucosa, eyes, genital mucosa)

Epidermolysis bullosa acquisita (EBA)

coexistence with lymproliferative disorders, autoimmune diseases, Crohn's disease , diabetes

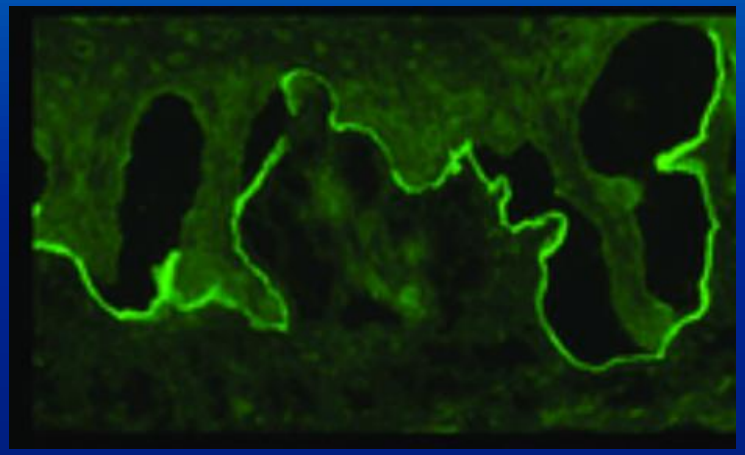


antibodies against collagen VII

Epidermolysis bullosa acquisita (EBA)
Diagnosis

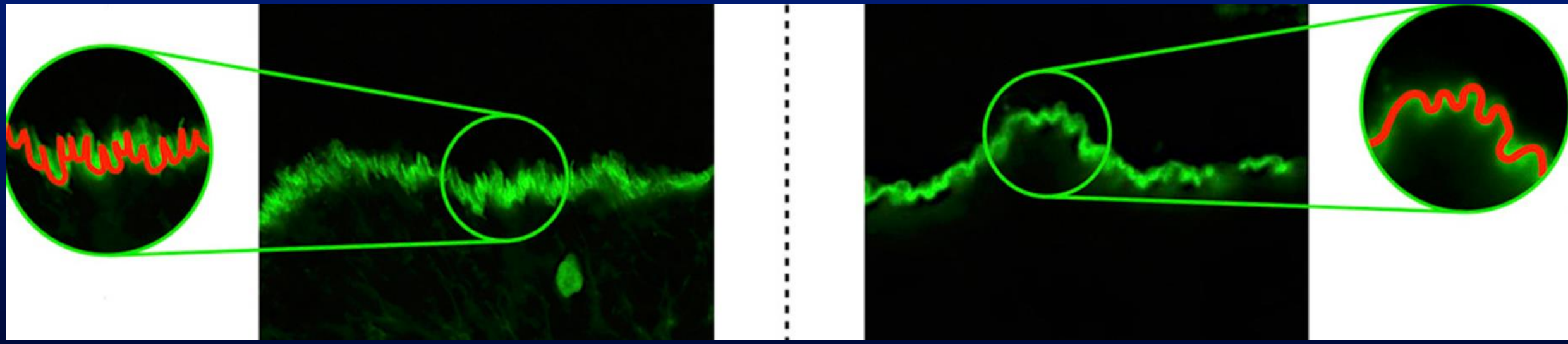
- DIF - linear IgG, C3 along the basement membranę zone
- IIF – IgG antibodies against basement membrane zone
- ELISA- anti-collagen VII antibodies

DIF



EBA

BP



„u” serrated pattern

„n” serrated pattern

Epidermolysis bullosa acquisita (EBA)
Treatment

- glucocorticoids, glucocorticoids and sulfones
- mycophenolate mofetil
- azathioprine
- cyclosporine
- methotrexate
- colchicine
- cyclophosphamide
- IVIG
- rituximab

Pemphigus

Pemphigus vulgaris

(vegetans, 20% herpetiformis)

Pemphigus foliaceus

(80% herpetiformis, erythematosus)

Paraneoplatic pemphigus

intraepidermal

Pemphigoid

Bullous pemphigoid

Mucous membrane pemphigoid

Pemphigoid gestationis

Dermatitis herpetiformis

Linear Ig A bullous dermatosis

Epidermolysis bullosa acquisita

subepidermal