

# Oral ulceration, vesiculobullous and dermatologic diseases.

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# Causes of oral ulceration (I)

## ■ Infective

Bacterial

Viral

Fungal

## ■ Traumatic

Mechanical

Chemical

Thermal

Factitious injury

Radiation

Eosinophilic ulcer (traumatic granuloma)

## ■ Idiopathic

Recurrent aphthous stomatitis

minor aphthous ulcers

major aphthous ulcers

herpetiform ulcers

# Causes of oral ulceration (II)

## ■ Associated with systemic disease

Haematological diseases

GIT diseases

Behcet's disease (syndrome)

HIV infection

Other diseases

## ■ Associated with dermatological diseases

Lichen planus

Chronic discoid lupus erythematosus

Vesiculobullous diseases

## ■ Neoplastic

Squamous cell carcinoma

Other malignant neoplasms

# Traumatic ulceration

- A cause of trauma must be identified
- The cause must fit the site, size, and shape of the ulcer
- On removal of the cause the ulcer must show signs of healing within 10 days

# Traumatic ulceration - remarks

- ***Mechanical injury***: often related to overextended flanges of a denture (diff. dg. neoplastic ulcer!)
- ***Radiation injury*** (delayed effects: epithelial atrophy, damage of vasculature; immediate effects: erythema, radiation mucositis, ulceration, oedema due to obstruction of lymphatics)
- ***Factitious ulcers*** (self-inflicted – manifestation of stress, anxiety, emotional disturbance,...)
- ***Eosinophilic ulcers*** (traumatic or eosinophilic granuloma of the tongue) ass. with trauma and crush injury of muscle – unknown etiology
- ***Chemical injury*** (caused also by chemicals used in dental practice, preparations used by patients in self-treatment, aspirin (oedema to epithelial necrosis))

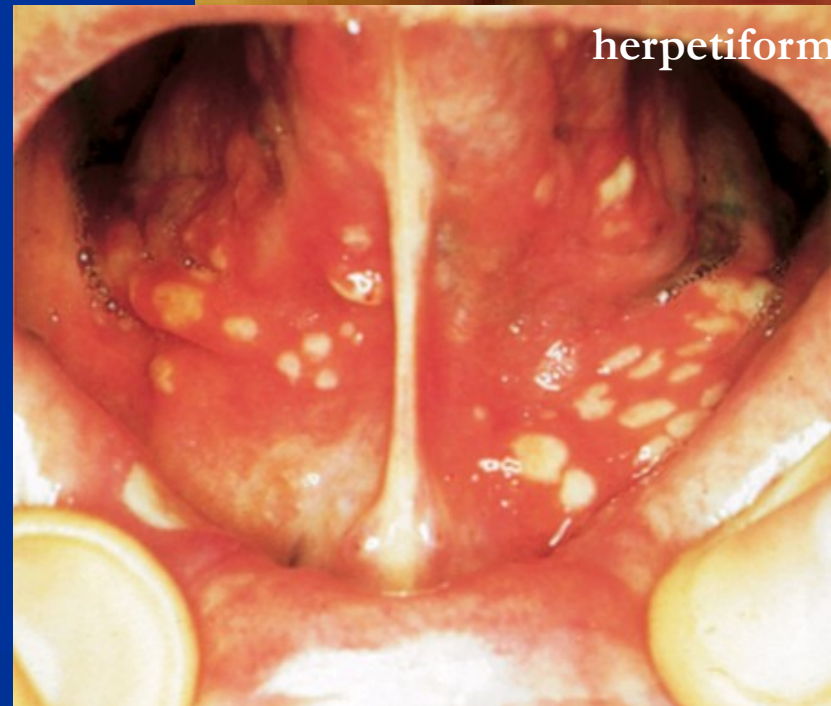
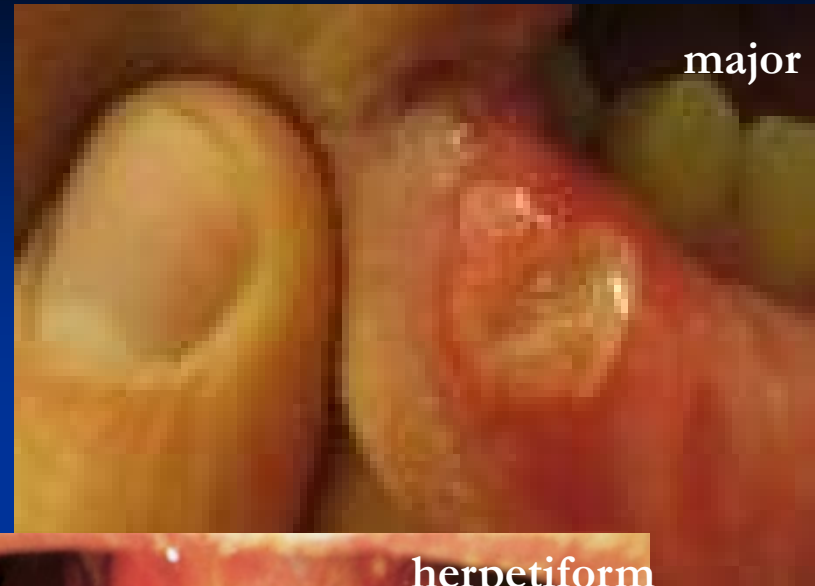
# Recurrent aphthous stomatitis (RAS): clinical variation

- **Minor aphthous ulcers** (80 %)
- **Major aphthous ulcers** (10 %)
- **Herpetiform ulcers**
  
- **Histopathology:** ulcerative lesion covered with fibrinopurulent membrane, mixed inflammatory infiltration; spongiosis of the epithelium

# Clinical features of RAS

	Minor	Major	Herpetiform
Age of onset	10-19	10-19	20-29
Number of ulcers	1-5	1-10	10-100
Size of ulcers (mm)	<10	>10	1-2, often coalesce
Duration (days)	7-14	>30	10-30
Principal sites	Lips, cheeks, tongue	As for minor+palate, pharynx	As for minor+floor of the mouth, palate, pharynx, gingiva

# Aphthous stomatitis





# Potential etiopathogenetic factors of RAS

- **Allergies**
- **Genetic predisposition** (HLA-B12, B51, Cw7)
- **Nutritional abnormalities** (B12, folate and iron deficiencies)
- **Haematological disorders** (anemia)
- **Gastrointestinal diseases** (avitaminosis B12 – atrophic oral mucosae, MAS, coeliac disease, ulcerative colitis, m. Crohn,...)
- **Hormonal influences** (pregnancy, luteal phase of MC,...)
- **Infectious agents** (L form of streptococci (hypersensitivity to *Streptococcus sanguis*), HSV, VZV, CMV,...)
- **Trauma**
- **Emotional stress**
- **Systemic disorders**

# RAS (recurrent aphthous ulcerations; canker sores)

## ■ Primary immunodysregulation

- In ulcerative stage: decreased ratio of CD4/CD8 T lymphocytes (about 1:10); increased TCR $\gamma\delta$ +, increased TNF- $\alpha$  → increased activity of T cell subpopulations that mediate cytotoxic damage
- Antibody-dependent cellular cytotoxicity, T-cell mediated cytotoxicity to oral epithelial cells (Ag unknown)??? cross reactivity between Ag shared by oral streptococci and oral epithelial cells???
- Patients with cyclic neutropenia

## ■ Decrease of mucosal barrier

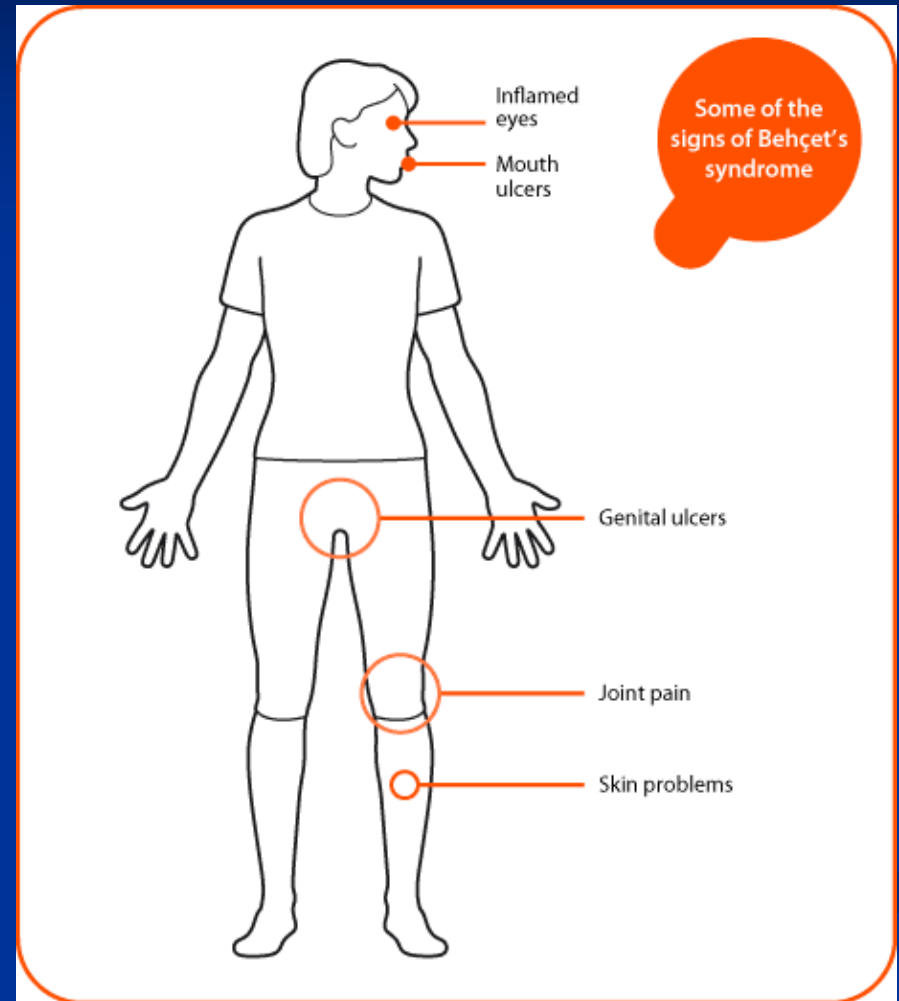
## ■ Increase in antigenic exposure

# Systemic diseases associated with RAS

- Behcet's syndrome (aphtous ulcers, genital ulcers, uveitis)
- Celiac disease (gluten intolerance)
- Cyclic neutropenia (AD, *ELA2* gene - neutrophil elastase)
- Nutritional deficiencies
- IgA deficiency
- Immunocompromised conditions, incl. HIV
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
- PFAPA syndrome (periodic fever, aphtous stomatitis, pharyngitis, cervical adenitis)
- Reiter's syndrome (arthritis, urethritis, conjunctivitis and skin lesions)

# Behcet's disease (syndrome)

- **Recurrent oral ulceration** (minor, major or herpetiform aphthae)
- + **two of the following:**
  - Recurrent genital ulcerations
  - Eye lesions (uveitis, retinal vasculitis,...)
  - Skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions, acneiform nodules,...)
- + arthritis, CNS involvement, cardiovascular, GIT, hematologic, pulmonary, muscular, renal systems involvement
- **HLA-B51**
- **Immunosuppressive treatment**



# Vesiculobullous diseases

## ■ Intraepithelial vesiculobullous diseases

**Acantholytic lesions** (produced by a breakdown of desmosomes)

pemphigus vulgaris

paraneoplastic pemphigus and other variants

Darier's disease

## **Non-acantholytic lesions**

viral infections of oral mucosae

## ■ Subepithelial vesiculobullous diseases

erythema multiforme

pemphigoid (mucous membrane, cicatrical)

dermatitis herpetiformis and linear IgA disease

epidermolysis bullosa

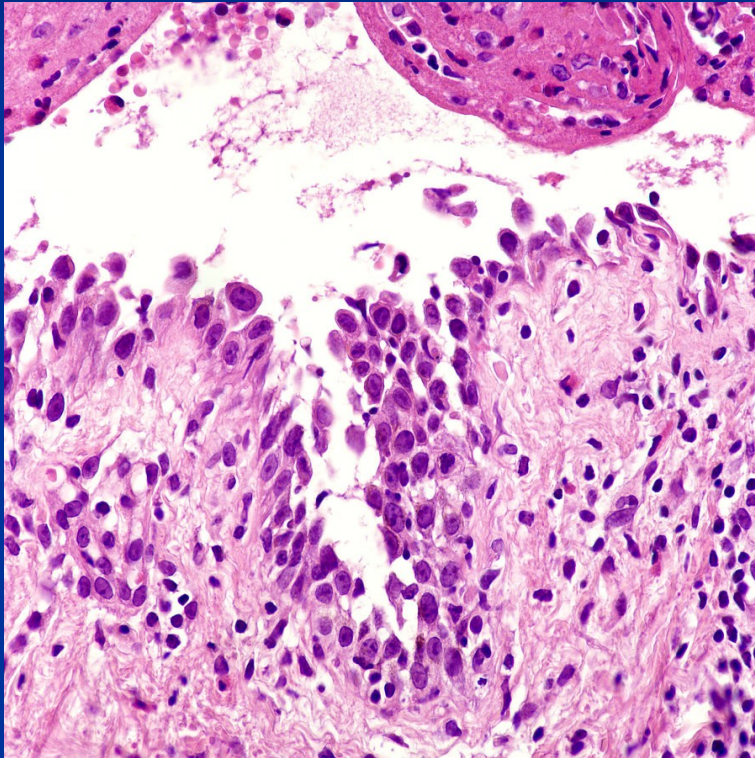
angina bullosa haemorrhagica (oral blood blisters)

bullous lichen planus

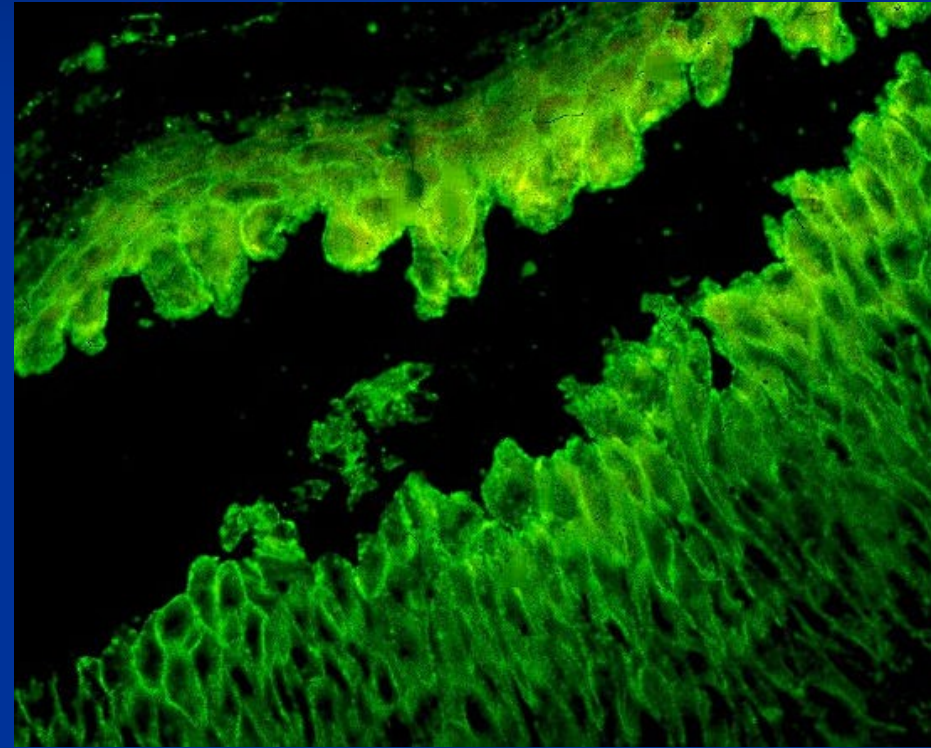
# Pemphigus vulgaris

- Intraepithelial, acantolytic vesicles and bullae involving skin and mucous membranes
- Ragged oral ulcers
- Oral lesions often the presenting feature
- Autoimmune disease - autoantibodies to desmosomal proteins (diagnostic test – direct immunofluorescence, IgG)
- Middle age, F>M, some ethnic groups frequently affected (genetic links)

# Pemphigus vulgaris



Suprabasal acantolysis, acantolytic bulla



IgG immunopositivity among keratinocytes

# Other forms of pemphigus, oral lesions

(antibodies against different proteins of desmosome complex)

- Pemphigus vegetans

(milder form, granulation tissue develop following rupture of bullae)

- Drug-induced pemphigus

(penicillamine, captopril,...)

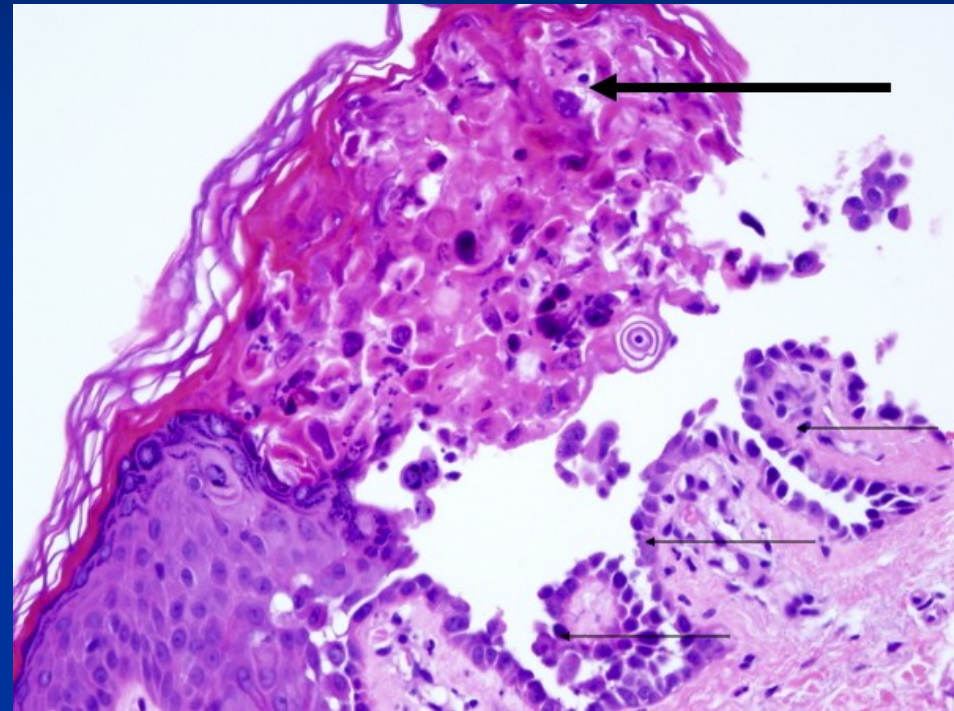
- Paraneoplastic pemphigus

(leukaemia, lymphoma,...)



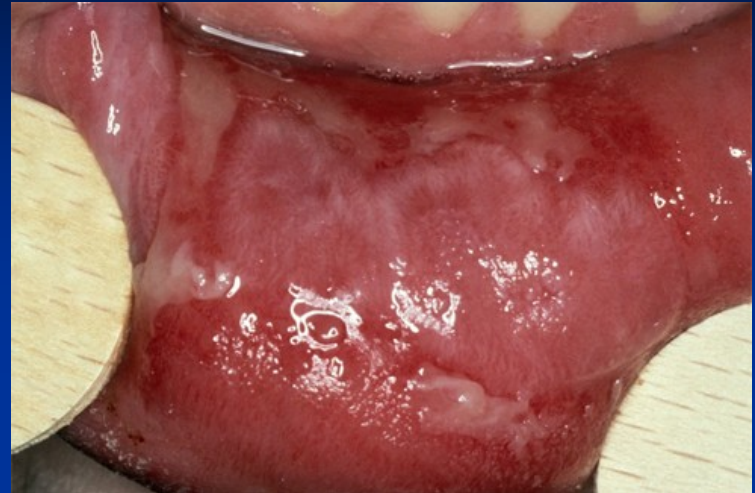
# Darier's disease (follicular keratosis)

- inherited disease - AD
- keratotic white coalescing papules skin (e.g. forehead, scalp; oral lesions in 50 % - hard palate and gingiva)
- intraepithelial acantholytic clefts with dyskeratotic cells



Acantholytic dyskeratosis with loss of cohesion between keratinocytes (thin arrows) and abnormal premature keratinization of epidermal cells (thick arrow)

# Erythema multiforme



- Mucosal vesicles and bullae variable; skin and mucous membranes
- Young adults, M>F
- Prodromal phase, severity variable (severe form: Stevens-Johnson sy (skin, oral, genital and ocular mucosae)
- Oral ulceration/circumoral crusting, haemorrhagic lesions
- Target/iris skin lesions
- Type III hypersensitivity reaction?, precipitated by drugs (sulphonamides)/infection (HSV)
- Immune complex vasculitis

# Pemphigoid: subtypes

- **Bullous pemphigoid**

(skin alone or with minimal mucosal involvement)

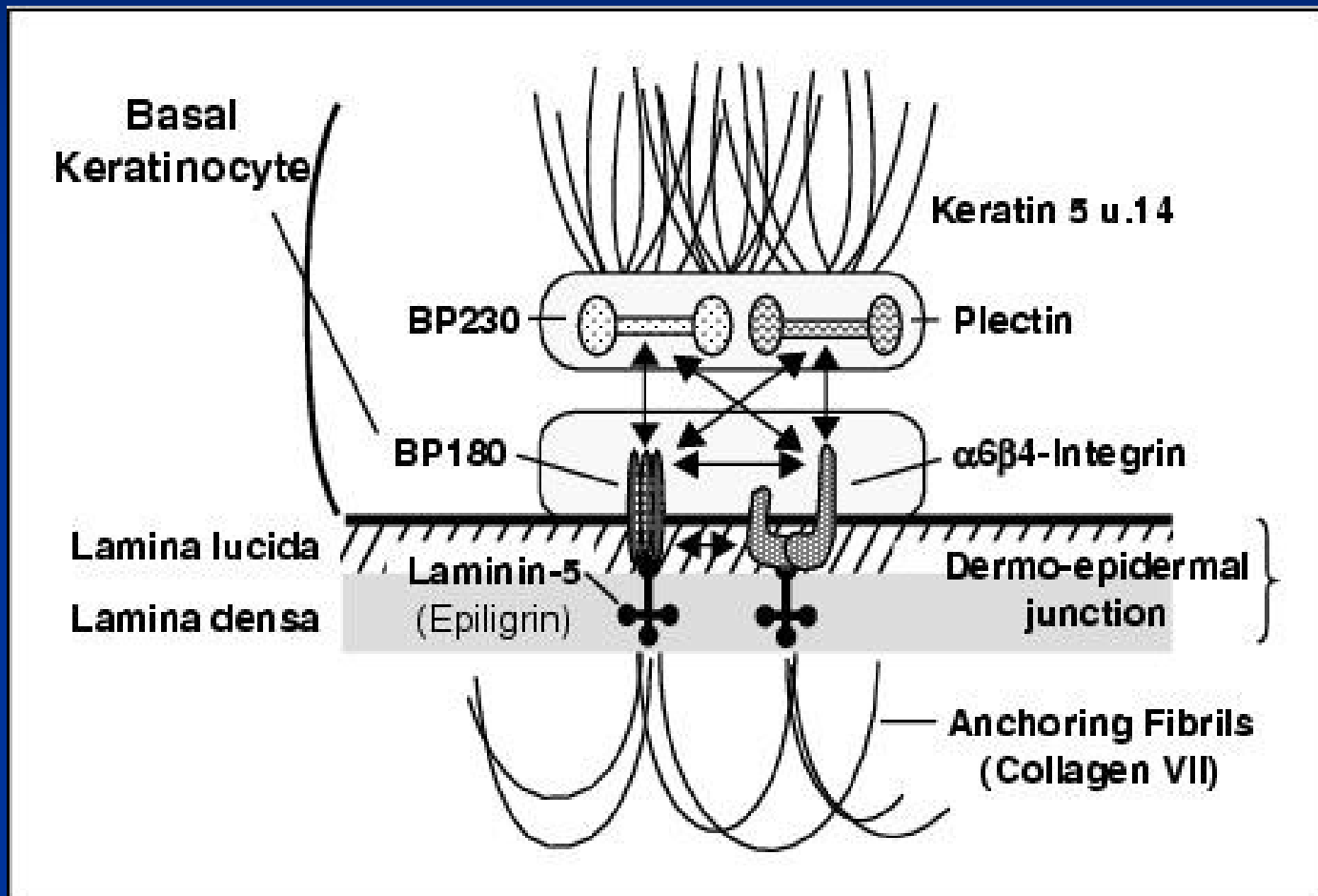
- **Mucous membrane pemphigoid**

(mucosa alone or with minimal skin involvement)

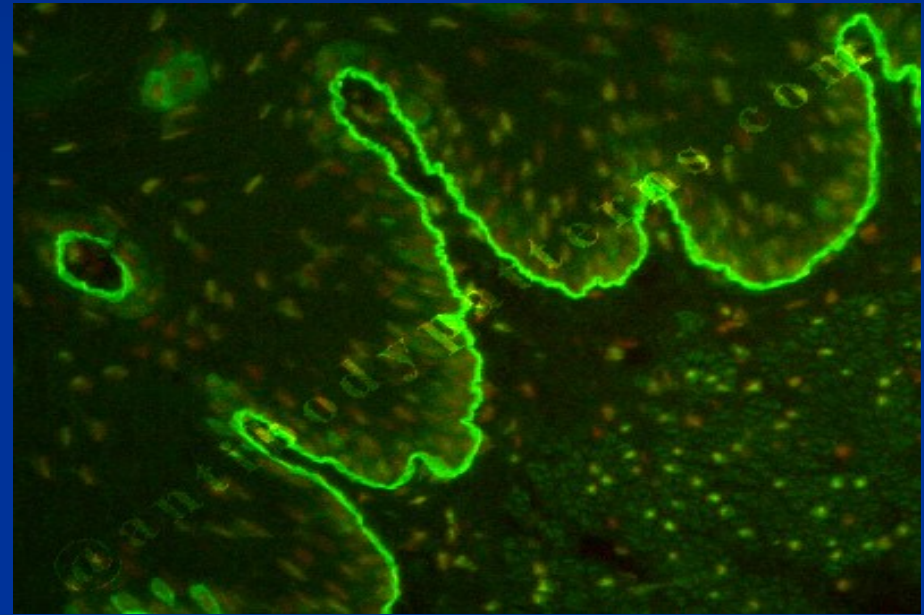
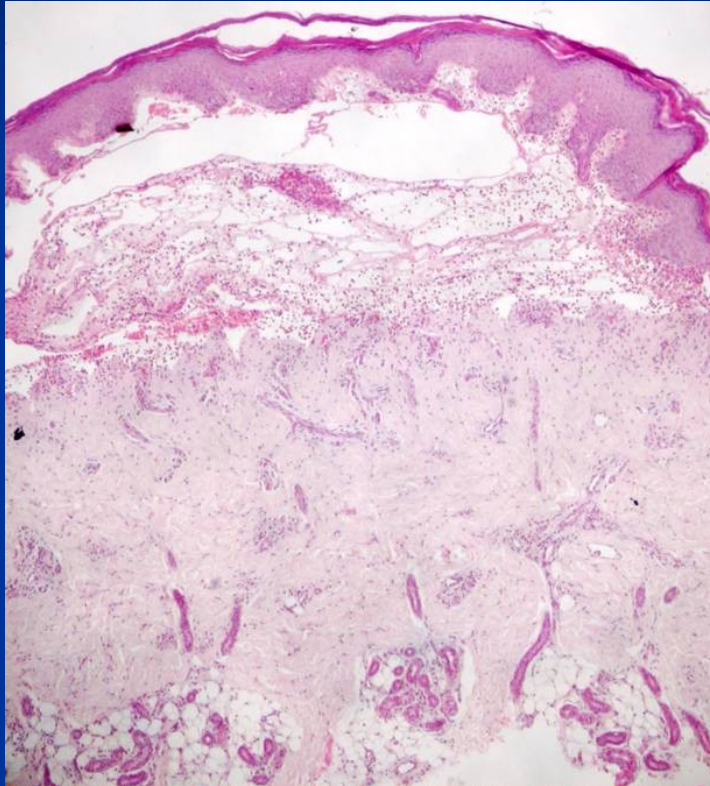
# Pemphigoid

- Complex group of subepithelial blistering diseases
- Autoantibodies attack hemidesmosome – basement membrane antigens (collagens, collagen-like proteins, laminins, integrins,..)
- Linear binding of IgG along the basement membrane
- Different clinical subtypes of pemphigoid reflect damage to different antigens
- Mucosal lesions, including mouth, occur predominantly in the mucous membrane pemphigoid subtypes

# Structural proteins of dermo-epidermal junction



# Pemphigoid



A – subepidermal bulla

B - linear, continuous deposition of IgG at the dermoepidermal basement membrane zone in perilesional skin

# Mucous membrane pemphigoid

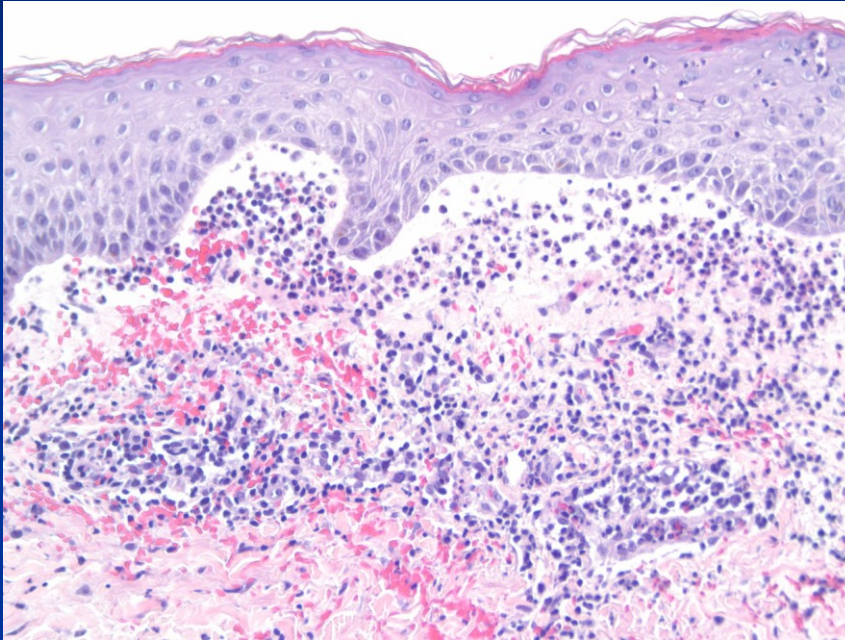
- mucosa alone or with minimal skin involvement
- conjunctiva, genital, nasal, laryngeal, oesophageal, pharyngeal mucose can be also affected
- Subepithelial vesicles and bullae; extensive ulceration, desquamative gingivitis, scarring (cicatrical MMP)
- older women (6th decade)
- autoantibodies to hemidesmosomal proteins

# Dermatitis herpetiformis

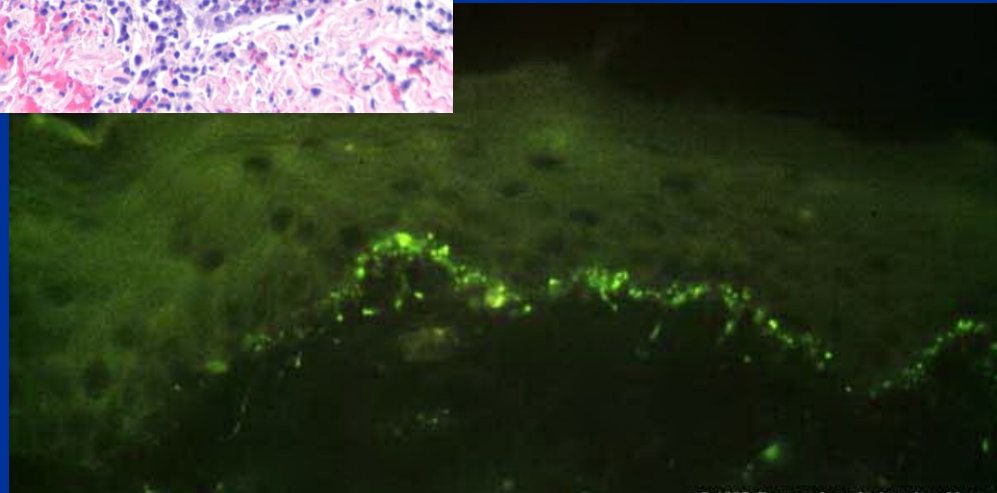
- Chronic, pruritic, subepidermal autoimmune blistering disease of the skin
- Oral manifestation variable  
(erythematous area → extensive erosions)
- Granular deposits of IgA in the tips of the connective tissue papillae together with complement components (activation of the alternative complement pathway by Ig A, chemotaxis of neutrophils)
- Associated with coeliac disease – gluten hypersensitivity



# Dermatitis herpetiformis



Subepidermal blister



Granular deposits of IgA in the tips of the connective tissue papillae

# Linear IgA disease

- Subepidermal blistering disease overlapping with dermatitis herpetiformis and bullous pemphigoid
- Oral lesions reported
- Linear binding of IgA along the basement membrane
- ass. with coeliac disease – gluten hypersensitivity

# Epidermolysis bullosa

- Inherited disease, 30 types
- Mutations in genes coding specific keratins in the basal epithelial layer (intraepithelial bullae), collagens and other attachment proteins (subepithelial bullae)
- Extreme fragility of the skin
- Mucosae also affected

EB type	EB subtype	Involved genes
<b>EBS</b>	EBS, Weber-Cockayne	K5, K14
	EBS, Koebner	K5, K14
	EBS, Dowling-Meara	K5, K14
	EBS with muscular dystrophy	plectin
<b>JEB</b>	JEB, Herlitz	laminin 5
	JEB, non-Herlitz	laminin 5, collagen XVII
	JEB with pyloric atresia	$\alpha 6\beta 4$ integrin
<b>DEB</b>	DDEB	collagen VII
	RDBE, Hallopeau-Siemens	collagen VII
	RDEB, non- Hallopeau-Siemens	collagen VII

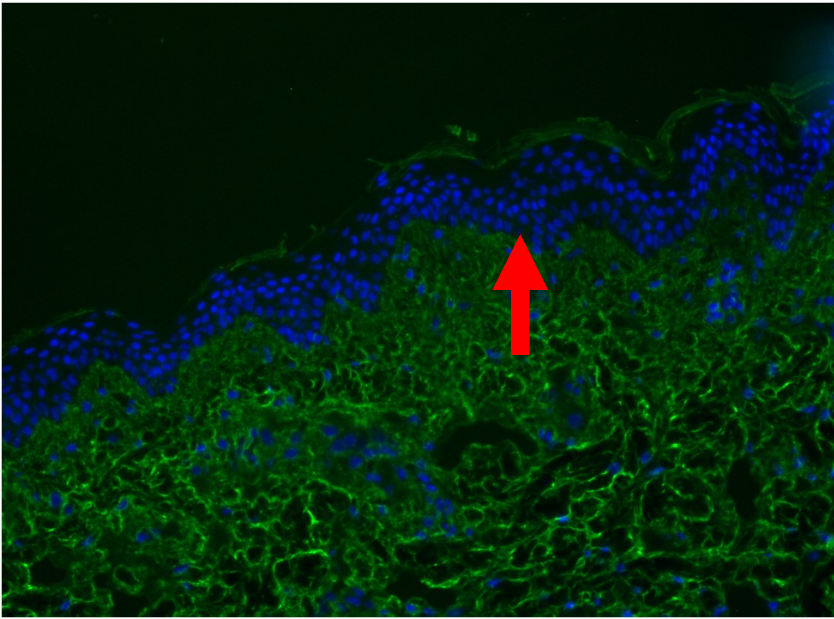
EBS, epidermolysis bullosa simplex

JEB, junctional epidermolysis bullosa

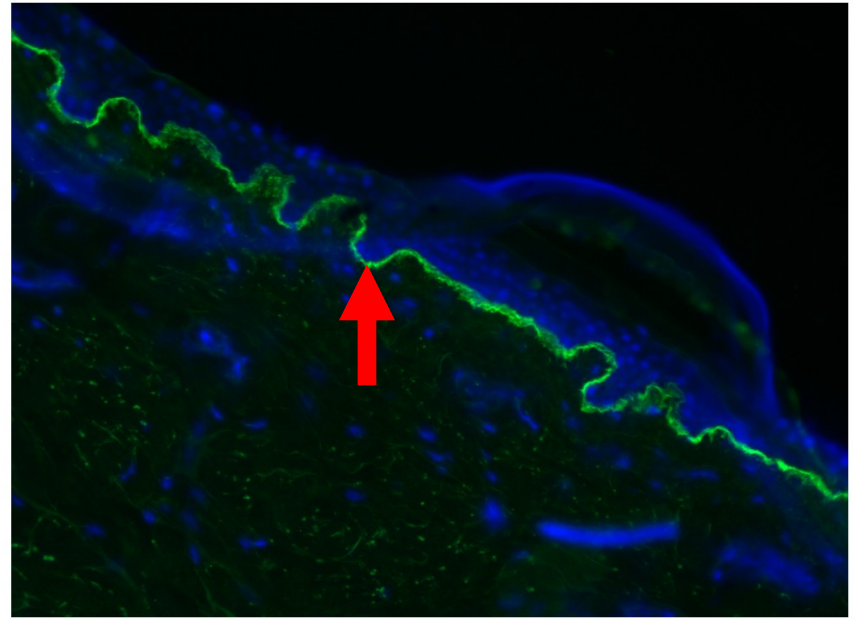
DDEB, dominant dystrophic epidermolysis bullosa

RDEB, recessive dystrophic epidermolysis bullosa

# Epidermolysis bullosa: immunofluorescence

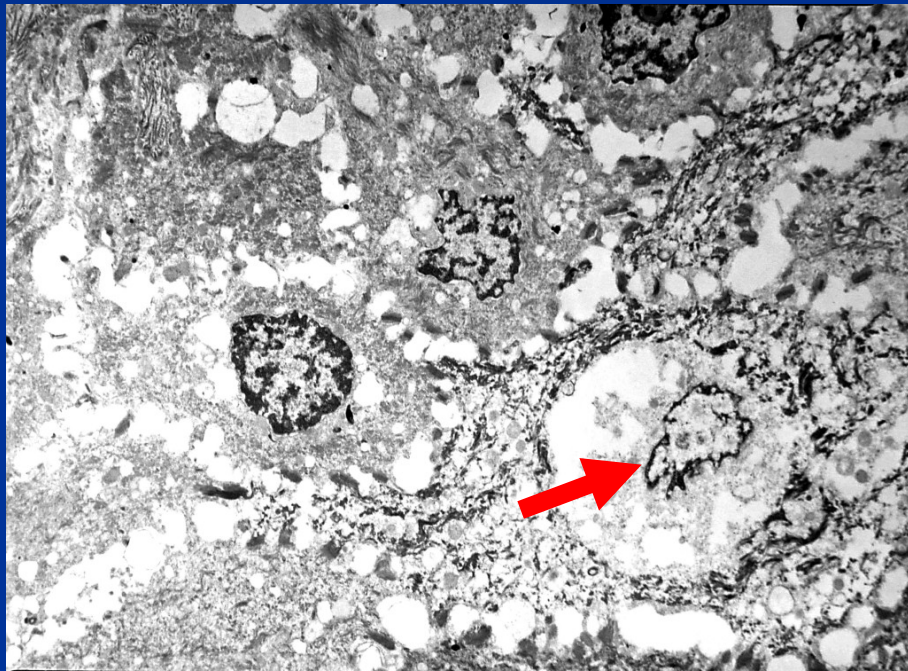


Absence of collagen VII in DE junction

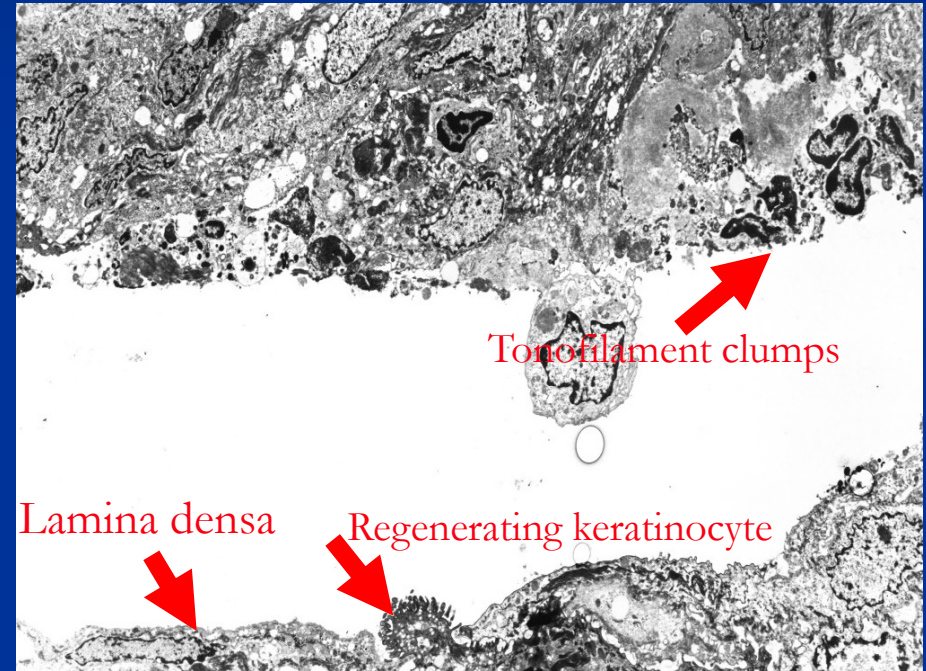


Normal control with presence of collagen VII

# Epidermolysis bullosa: ultrastructural examination

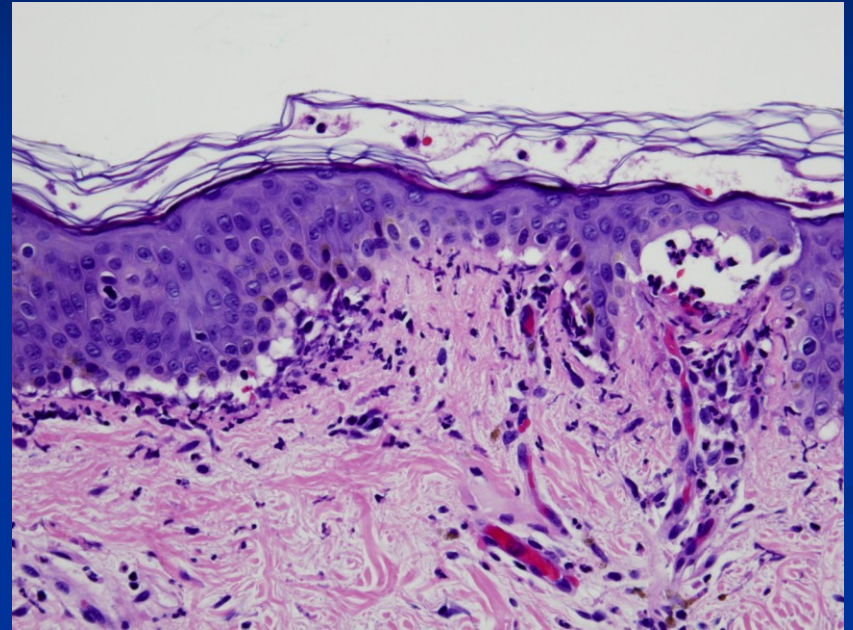


Lysis of keratinocytes in EB dystrophica



EB simplex

# Epidermolysis bullosa acquisita



- Autoimmune blistering
- Subepithelial bullae, oral lesion also
- Linear binding of IgG and C3 along the basement membrane

# Angina bullosa haemorrhagica (oral blood blister)

- Spontaneous blood-filled subepithelial bullae on the oral mucosa
- Solitary, in adults
- 2-3 cm in diameter
- Soft palate most often affected
- Perforation and uneventful healing
- Etiology unknown????, immunological findings negative



# Oral lichen planus

- Alone or associated with skin lesions
- F>M; adults 3rd-5th decade
- Usually bilateral mucosal oral lesions
- Non-erosive forms symptomless
- Buccal mucosa mostly affected
- Gingival lesions presented as desquamative gingivitis

# Aetiology of lichen planus

- Aetiology not fully understood – cell-mediated immune responses to an external antigen, or to internal antigenic changes in the epithelial cells (T-cell mediated, resembles type IV hypersensitivity reaction, CD8+ T cells damage basal epithelium)
- Often associated with other systemic disease
- May be associated HCV
- May be a part of GVHD (graft versus host reaction in recipients of transplants)
- Differential diagnosis: lichenoid reactions – hypersensitivity to drugs or dental materials

# Clinical type of lichen planus

- Reticular (lace-like striae)
- Atrophic (resemble erythroplakia)
- Plaque-like (resemble leukoplakia)
- Papular
- Erosive
- Bullous

# Lichen planus morphology and histopathology

- Violaceous, itchy papule with white streaks on the surface (Wickham's striae)
- Papules have a variable pattern (discrete, annular, linear, widespread rash,...)
- Typically flexor surface of the wrists affected, fingernail also affected (10 %); skin LP – 85 % resolve in 18 months; oral LP more chronic
- Ortho- or parakeratinized surface
- Acanthotic or atrophic epithelium
- Subepithelial band of T lymphocytes
- Liquefactive degeneration of basal cells

# Oral lichen planus

