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 overxtended flanges of a denture (diff. dg. neoplastic ulcer!)
- ***Radiation injury*** (delayed effects: epithelial atrophy, damage of vasculature; immediate effects: erythema, radiation mucositis, ulceration, oedema dueto 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

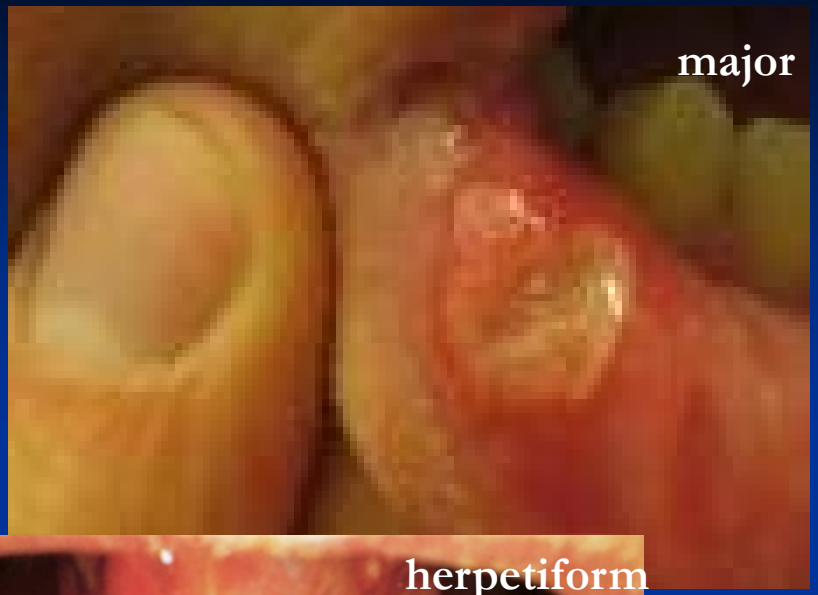
- **Minor aphthous ulcers** (80 %)
- **Major aphthous ulcers** (10 %)
- **Herpetiform ulcers**

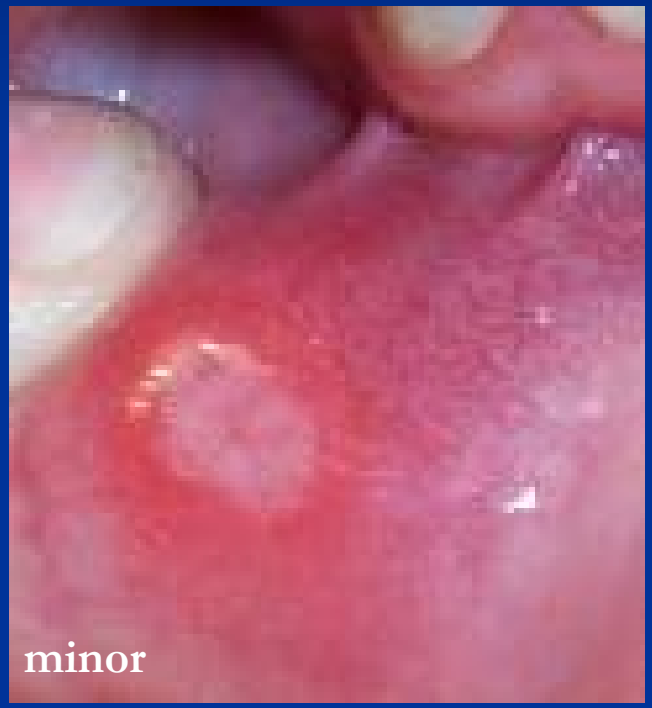
- **Histopathology:** ulcerative lesion covered with fibrinopurulent membrane, mixed inflammatory infiltration; spongiosis of the epithelium

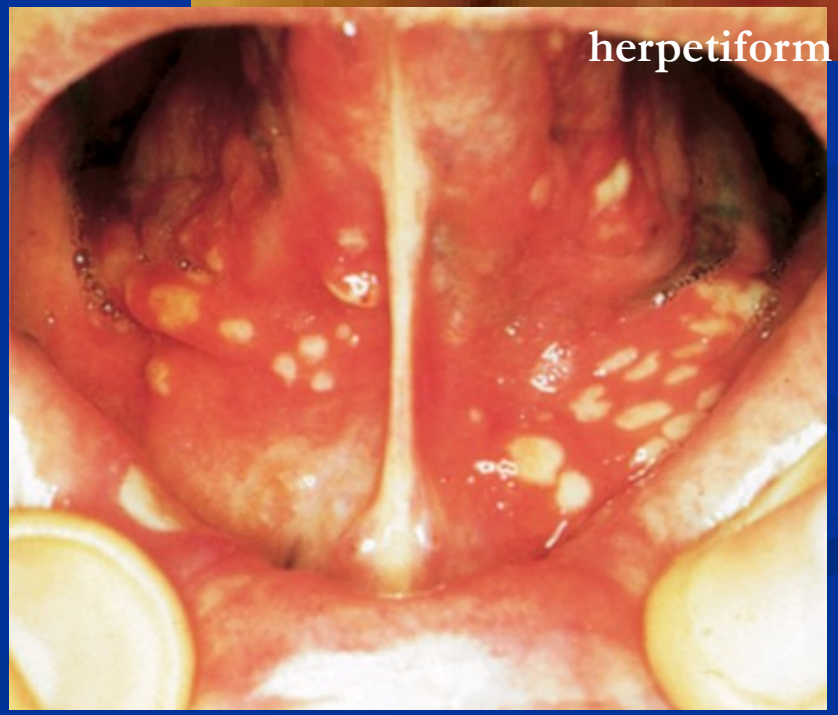
Clinical features of RAS

	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

Aphtous stomatitis







Potential etiopathogenetic factors of RAS

- **Allergies**
- **Genetic predisposition** (HLA-B12, B51, Cw7)
- **Nutritional abnormalities** (B12, folate and iron deficiences)
- **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 TCRγδ+, increased TNF-α → 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)

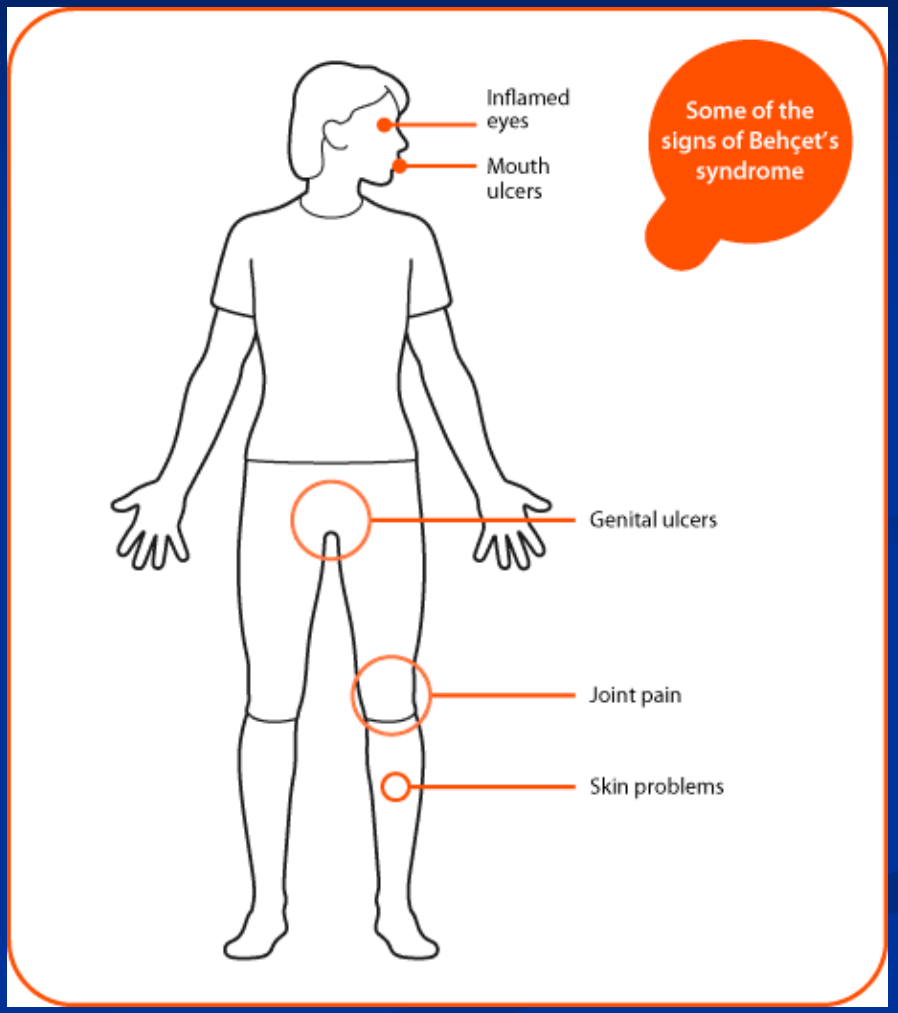
- **Recurrent oral ulceration** (minor, major or herpetiform aphthae)

+ 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**
- **Immunosuppresive 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

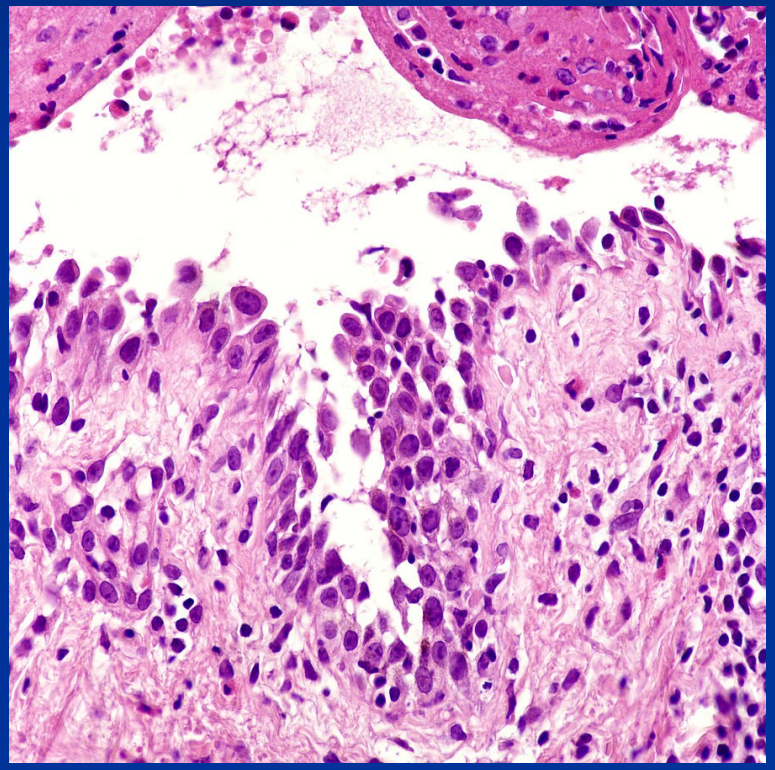
angina bullosa haemorrhagica (oral blood blisters)

bullous lichen planus

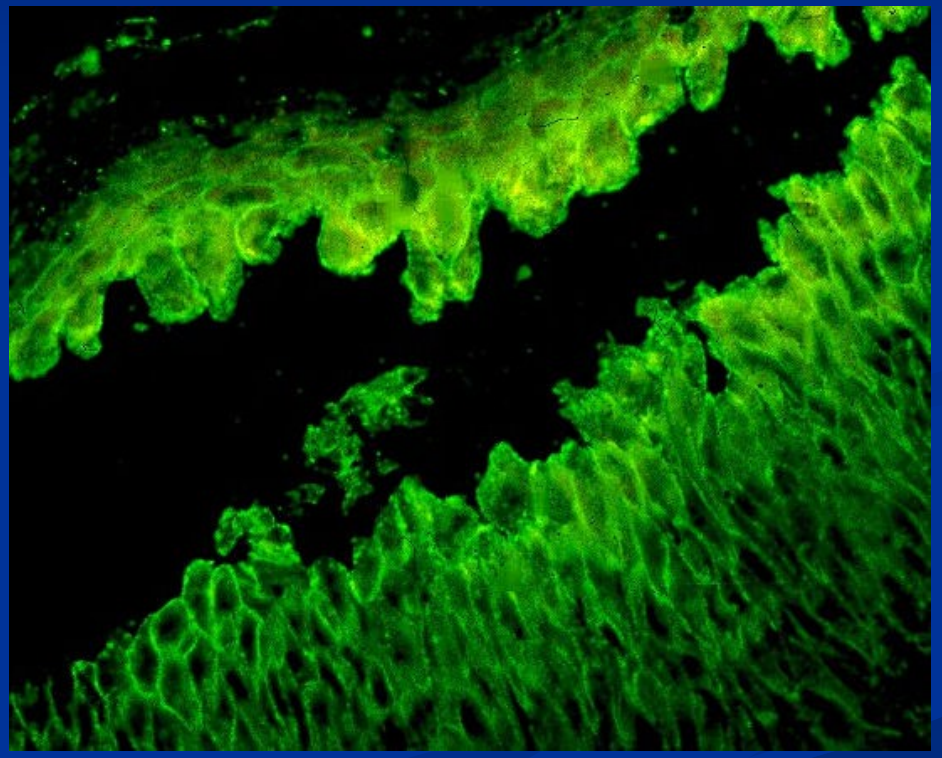
Pemphigus vulgaris

- 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 immunopositivita 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

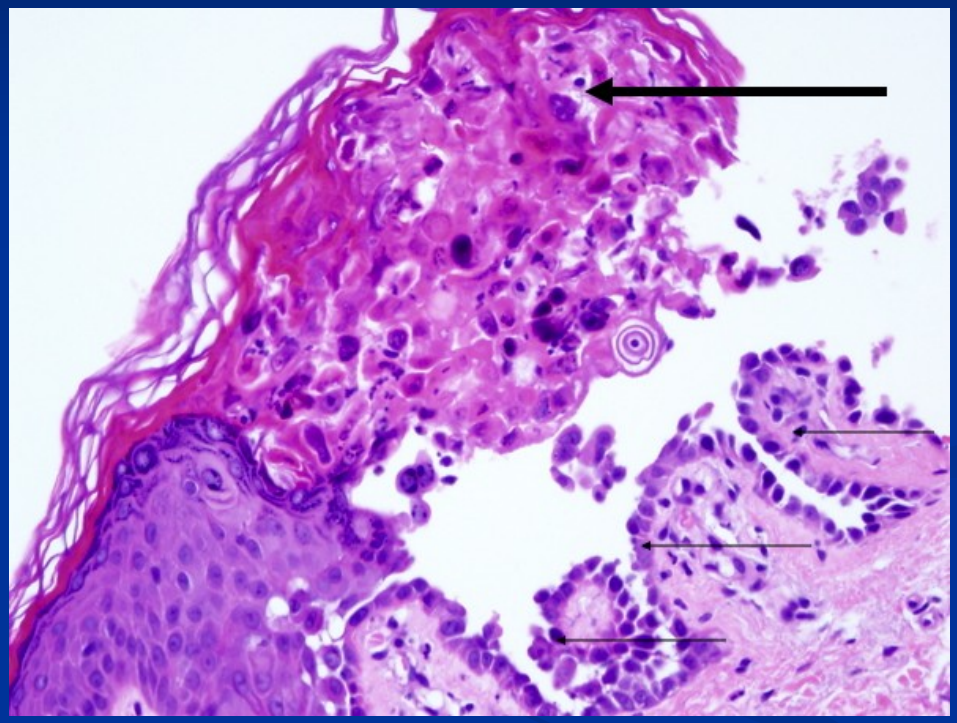
  (penicillamine, captopril,…)

- Paraneoplastic pemphigus

  (leukaemia, lymphoma,…)

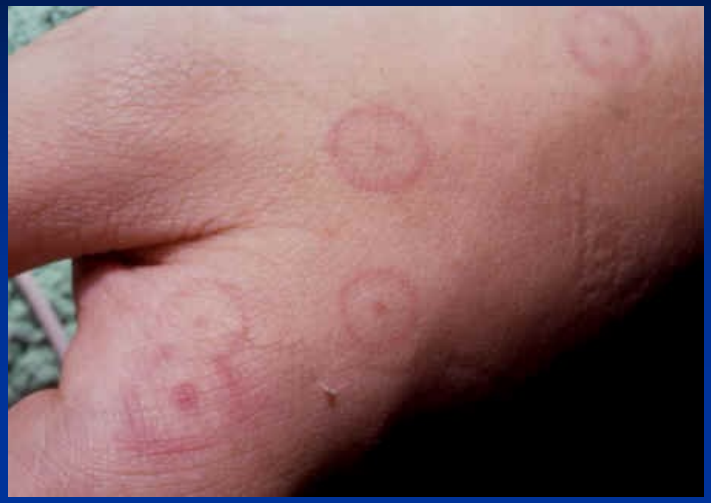
Darier´s disease (follicular keratosis)

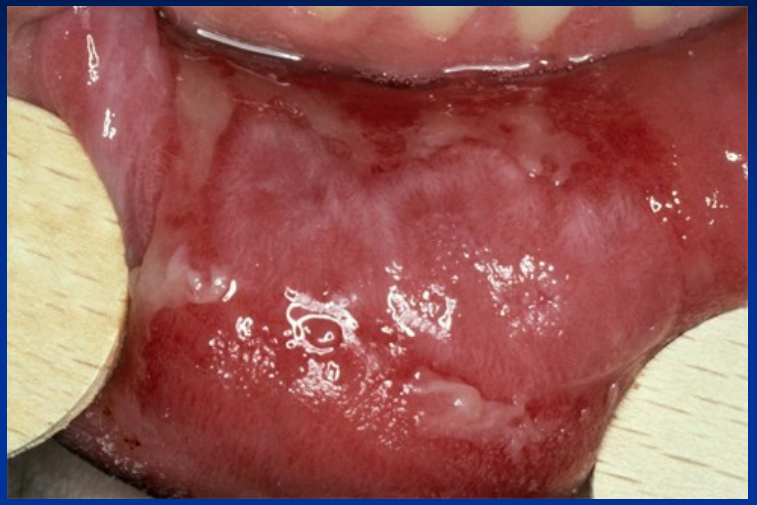
- inherited disease - AD
- keratotic white coalescing papules skin (e.g. forehead, scalp; oral lesions in 50 % - hard palate and gingiva)
- intraepithelial acantholytic clefts with dyskeratotic cells



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)

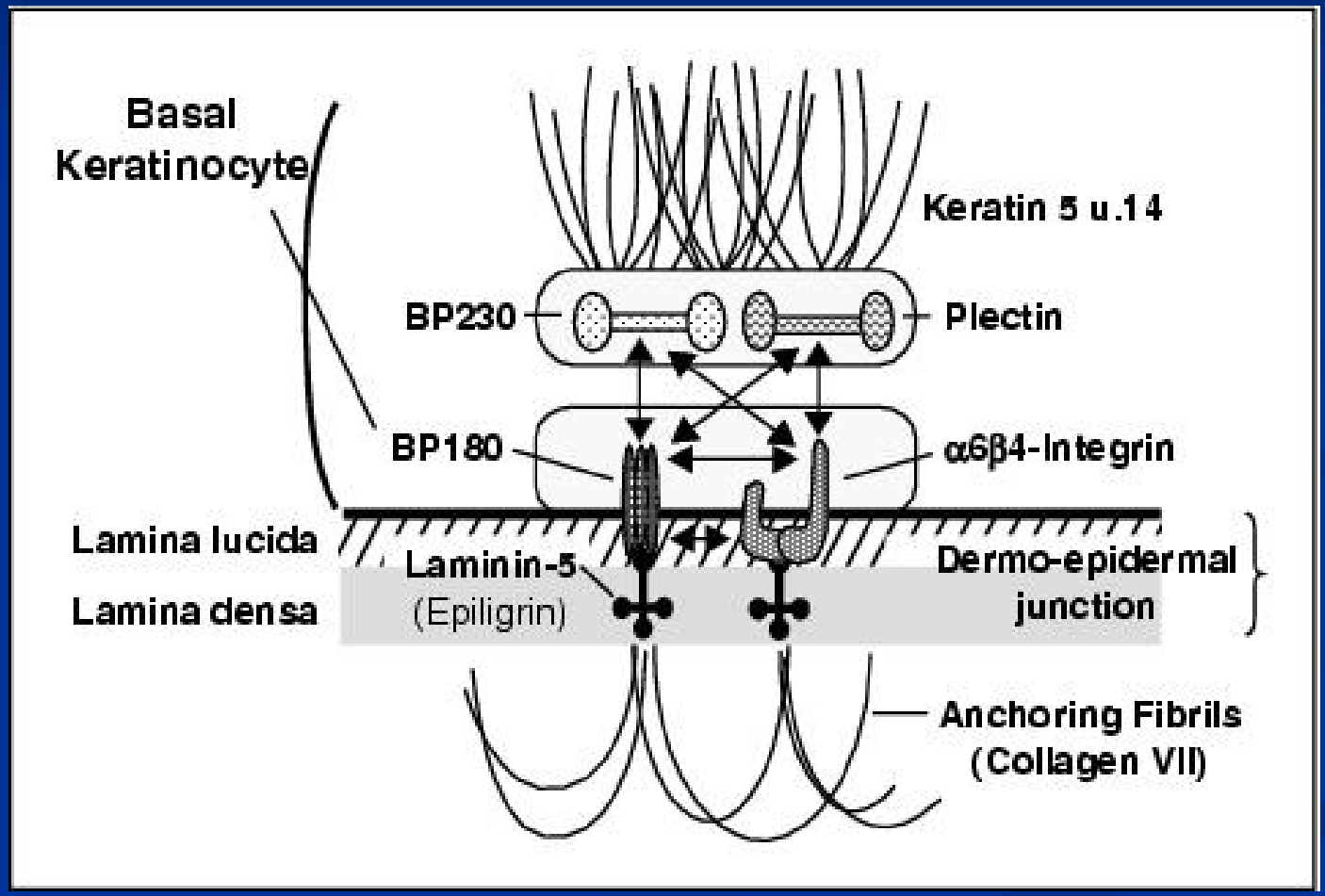
- **Mucous membrane pemhigoid**

(mucosa alone or with minimal skin involvement)

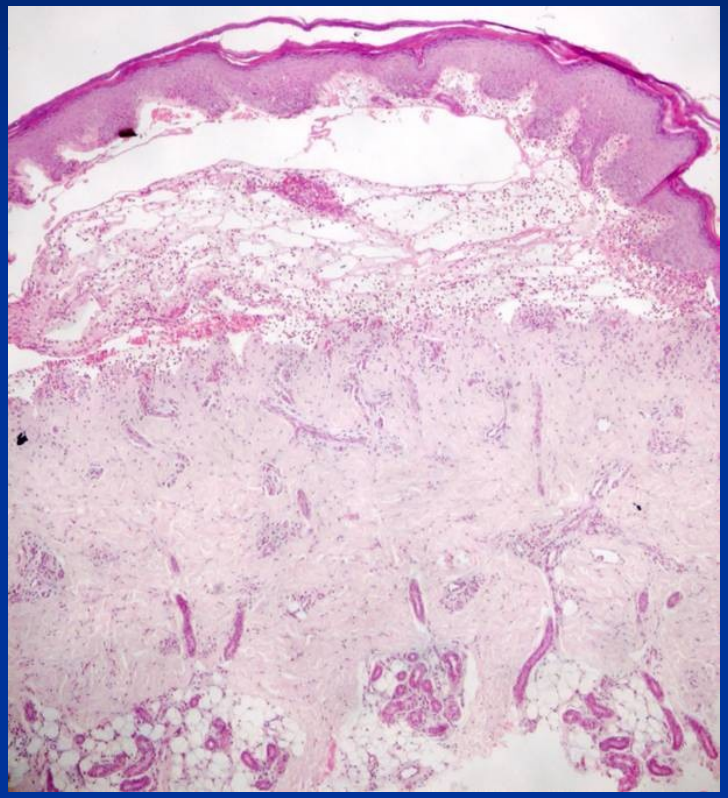
Pemphigoid

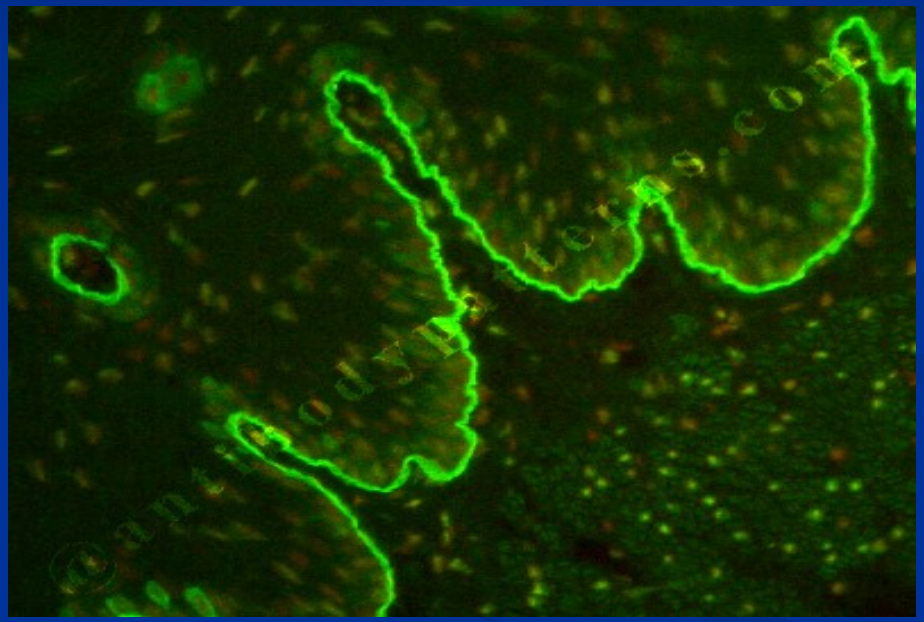
- Complex group of subepithelial blistering diseases
- Autoantibodies attack hemidesmosome – basement membrane antigens (collagens, collagen-like proteins, laminins, integrins,..)
- Linear binding of IgG along the basement membrane
- Different clinical subtypes of pemphigoid reflect damage to different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

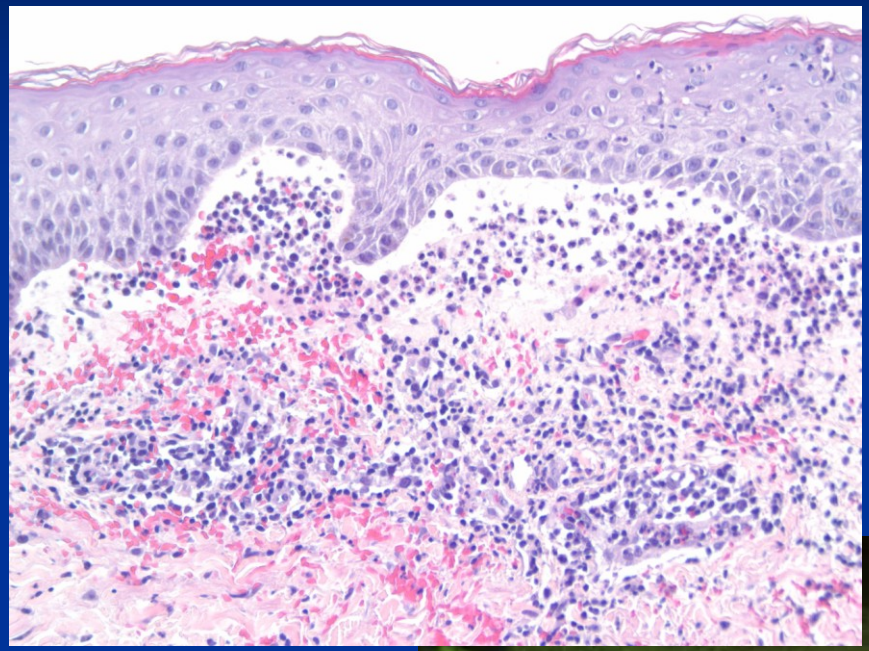
- mucosa alone or with minimal skin involvement
- conjunctiva, genital, nasal, laryngeal, oesophageal, pharyngeal mucose can be also affected
- Subepithelial vesicles and bullae; extensive ulceration, desquamative gingivis, scarring (cicatrical MMP)
- older women (6th decade)
- autoantibodies to hemidesmosomal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

Dermatitis herpetiformis

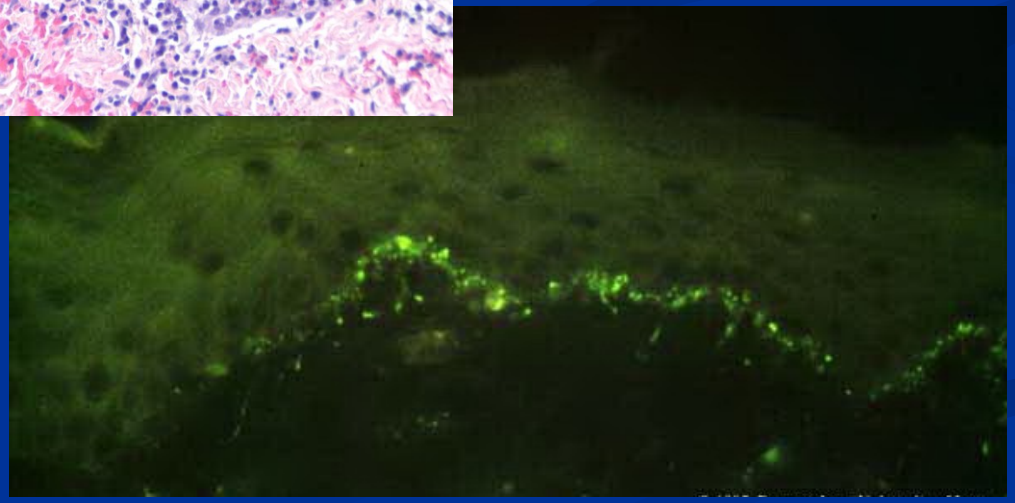
- Chronic, pruritic, subepidermal autoimmune blistering disease of the skin
- Oral manifestation variable

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

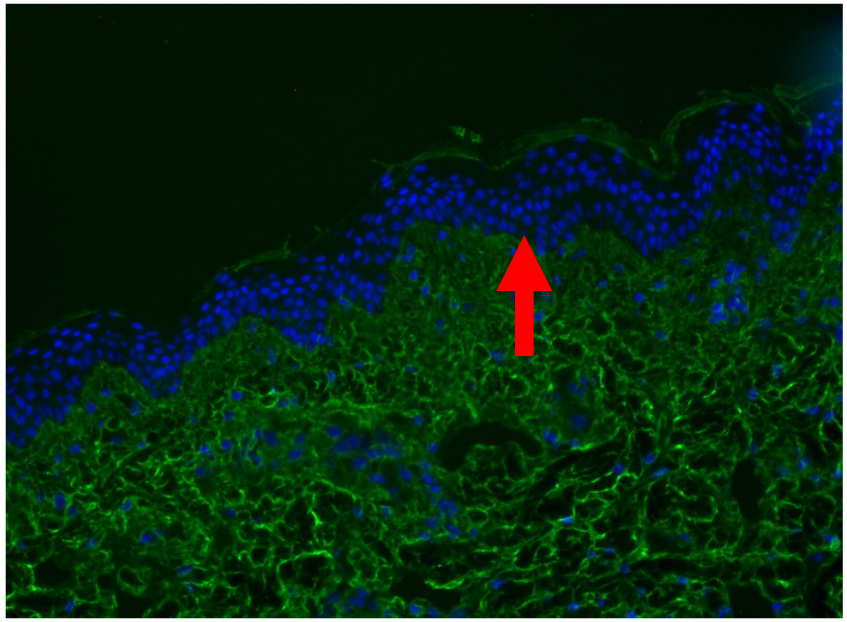
Epidermolysis bullosa

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

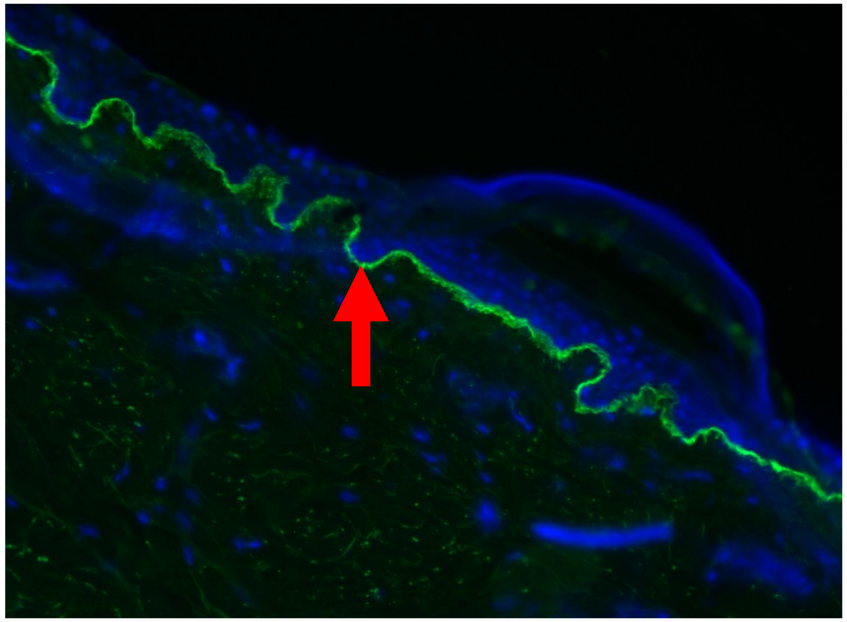
EB type	EB subtype	Involved genes
EBS	EBS, Weber-Cockayne	K5, K14
	EBS, Koebner	K5, K14
	EBS, Dowling-Meara	K5, K14
	EBS with muscular dystrophy	plectin
JEB	JEB, Herlitz	laminin 5
	JEB, non-Herlitz	laminin 5, collagen XVII
	JEB with pyloric atresia	α6β4 integrin
DEB	DDEB	collagen VII
	RDBE, Hallopeau-Siemens	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

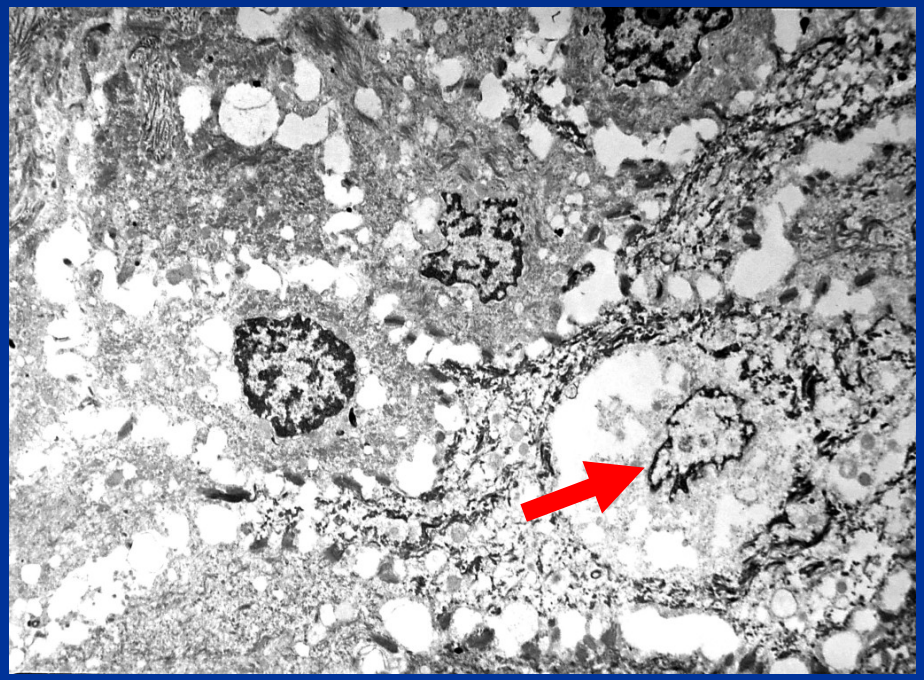


Absence of collagen VII in DE junction

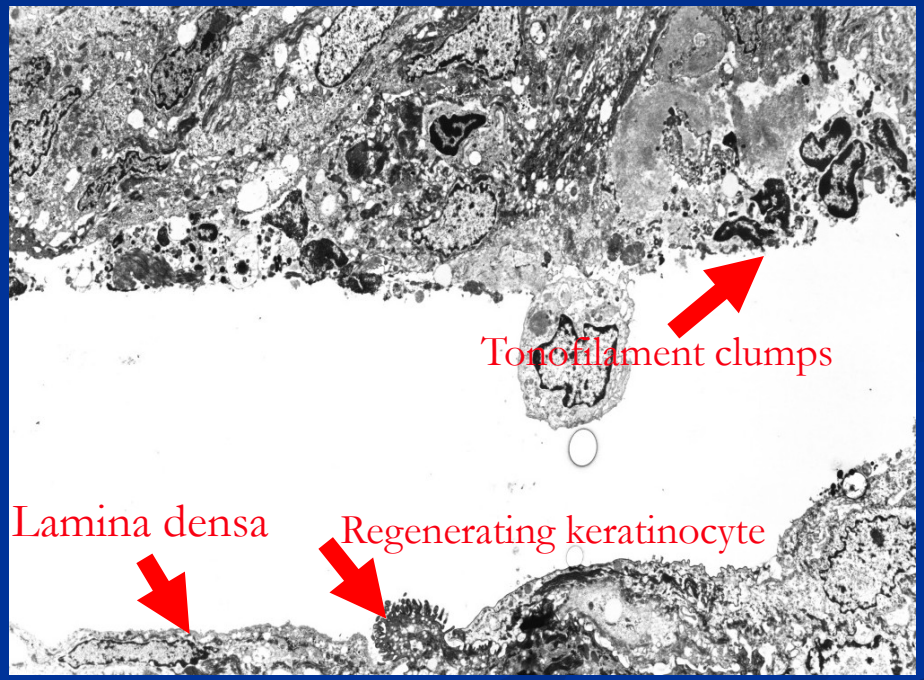


Normal control with presence of collagen VII

Epidermolysis bullosa: ultrastructural examination

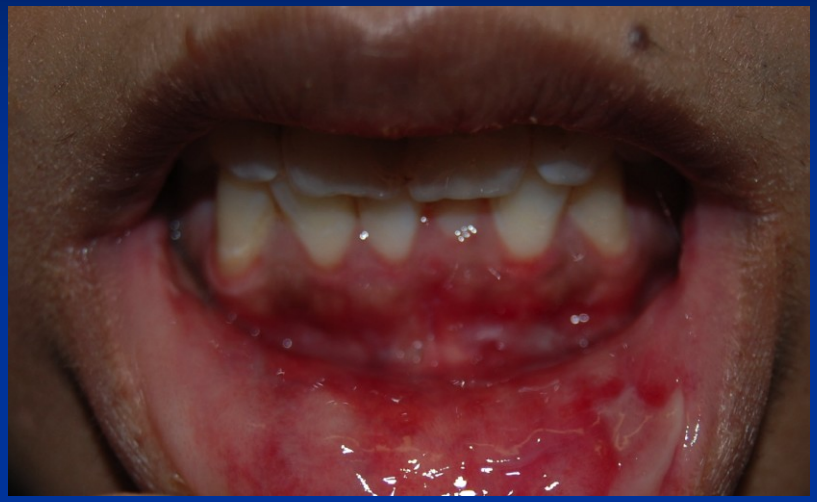


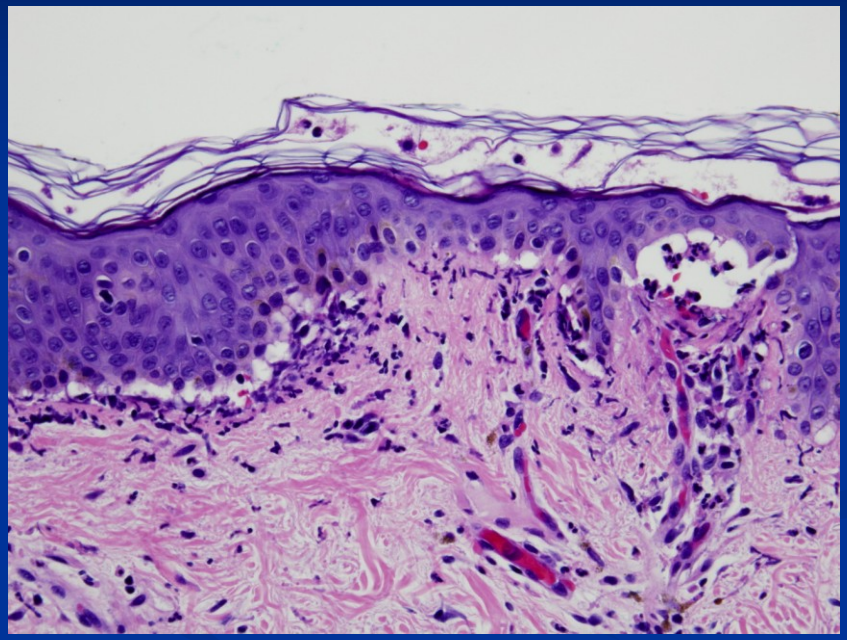
Lysis of keratinocytes in EB dystrophica



EB simplex

Epidermolysis bullosa acquisita





- Autoimmune blistering
- Subepithelial bullae, oral lesion also
- Linear binding of IgG and C3along the basement membrane

Angina bullosa haemorrhagica (oral blood blister)

- Spontaneous blood-filled subepithalial bullae on the oral mucosa
- Solitary, in adults
- 2-3 cm in diameter
- Soft palate most often affected
- Perforation and uneventfull 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

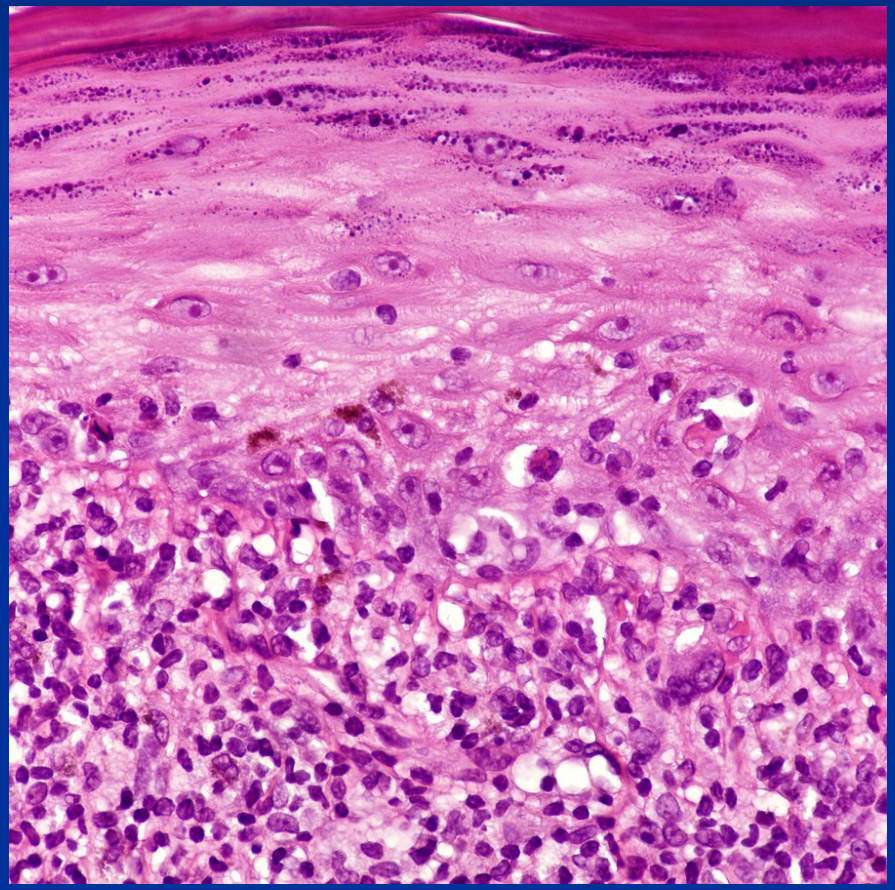
Clinical type of lichen planus

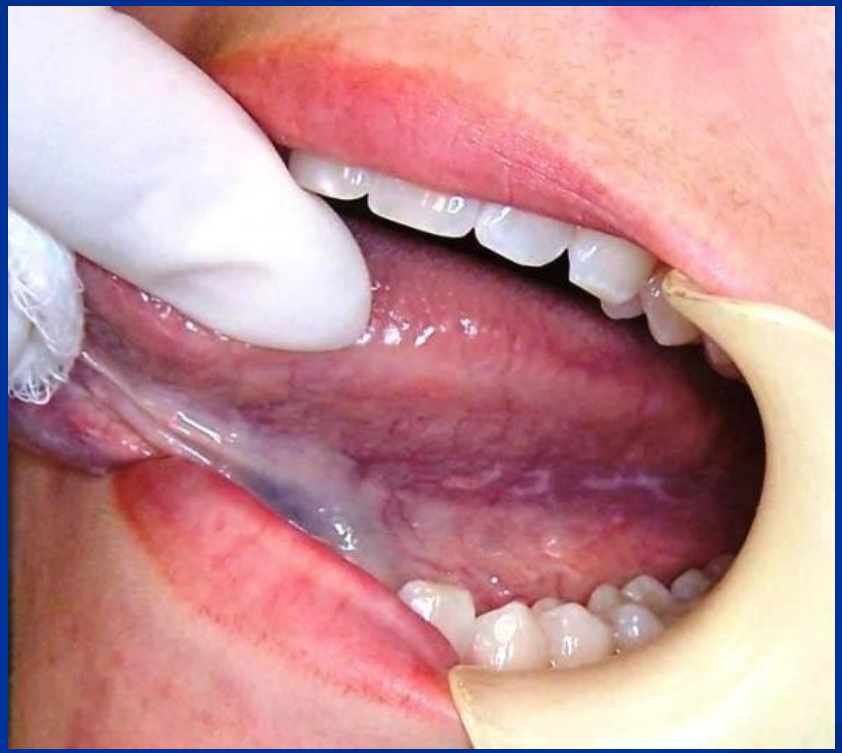
- Reticular (lace-like striae)
- Atrophic (resemble erythroplakia)
- Plaque-like (resemble leukoplakia)
- Papular
- Erosive
- Bullous

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





Thanks for your attention……..