

Keratosis and precancerous and premalignant lesions and conditions.

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Keratoses

- Increase and/or abnormal keratin production
- Not removed by scraping
- Classified on basis of aetiology

Histopathological terms

- Orthokeratosis
- Parakeratosis
- Hyperkeratosis
- Hyperparakeratosis
- Acanthosis
- Epithelial atrophy
- Cellular atypie
- Epithelial dysplasia

Precancerous and premalignant lesions and conditions: pre-malignant and tissue lesions and changes with statistically increased risk of progression to cancer

■ Precancerous/premalignant lesions:

- dysplasia/intraepithelial neoplasia
- *in situ* carcinoma
- actinic keratosis (lips)

■ Precancerous conditions/facultative precanceroses

- morphologically and cytologically still no signs of neoplastic transformation, but in these lesions statistically significant increased risk of cancer

Precancerous/premalignant lesions:

- **Dysplasia/intraepithelial neoplasia:** loss of uniformity and architectural arrangement of epithelial cells
- Progression of dysplastic changes/intraepithelial neoplasias in invasive cancer:
low grade dysplasia → high grade dysplasia → *carcinoma in situ* → invasive carcinoma (with invasion through basement membrane)
- *carcinoma in situ*: dysplastic changes involve all thickness of the epithelium – preinvasive neoplasia – high risk of progression into invasive carcinoma
- most low grade dysplasias do not progress into carcinoma, but the risk of progression of high grade dysplasias and in situ carcinomas is very high

Precancerous conditions/facultative precanceroses

- Conditions assoc. with epithelial atrophy (e.g. siderophenic dysphagia)
- Oral submucous fibrosis
- Lichen planus
- Lupus erytematodes
- Epidermolysis bullosa
- Xeroderma pigmentosum (AR, defect of DNA reparation)

Aetiological classification of white lesions of the oral mucosa

■ Hereditary

- oral epithelial naevus (white sponge nevus); AD, genes encoding CK 4 and 13 mutated
- oral manifestation of other rare genodermatoses
- leukoedema (in persons with racial pigmentation; whiteness of slightly folded mucosa)

■ Traumatic (mechanical – frictional keratosis, chemical, thermal injury, nicotinic stomatitis)

■ Infective

- Candidosis
- Syphilitic leukoplakia
- Hairy leukoplakia

■ Idiopathic (leukoplakia)

■ Dermatological

- Lichen planus
- Lupus erythematosus

■ Neoplastic

- Carcinoma *in situ*
- SCC

Genodermatoses

■ Pachyonychia congenita

- AD, thickening of nail, oral white lesions

■ Dyskeratosis congenita

- ?, M, skin pigmentation, dystrophic nails, mucosal hyperkeratosis, gingivitis/periodontal destruction, premalignant hyperkeratotic lesions

■ Tylosis

- AD, hyperkeratosis palms/soles; predisposes to oesophageal ca, oral hyperkeratosis

■ Hereditary benign intraepithelial dyskeratosis

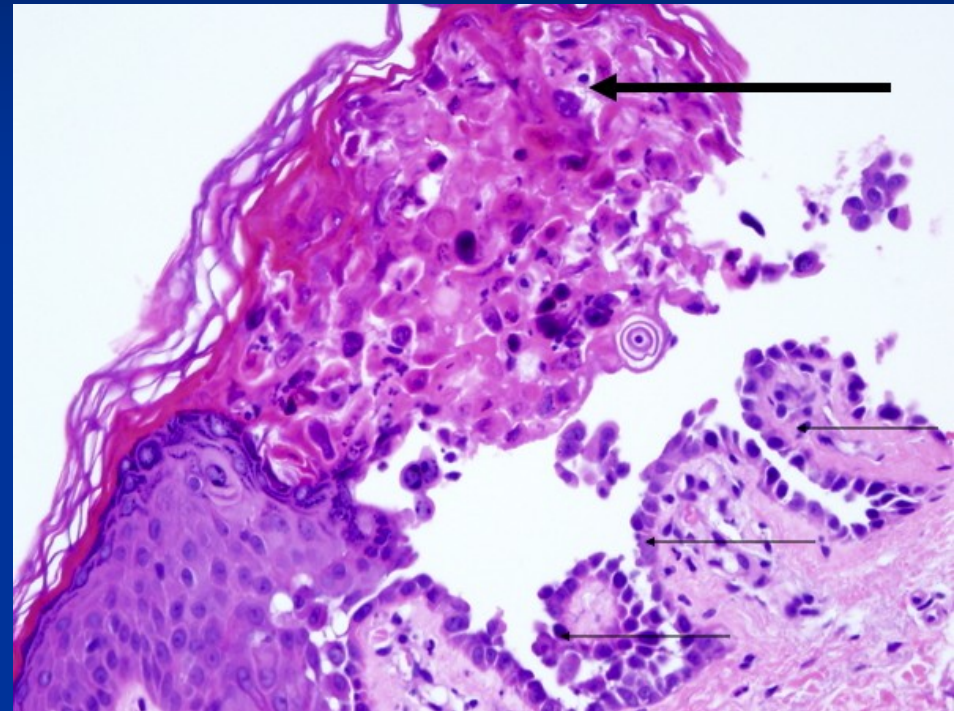
- AD, US, oral epithelial naevus-like lesion, premature keratinisation-dyskeratosis

■ Follicular keratosis (Darier's disease)

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

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)

Leukoplakia

- WHO definition: white patch or plaque that cannot be characterized clinically or histopathologically as any other disease
- Dysplastic or non-dysplastic

Leukoplakia

- The diagnosis of leukoplakia is one of the exclusion
- It is a clinical diagnosis
- It has no histological connotation
- Epithelial dysplasia may or may not be present (may be precancerous)
- The severity of dysplasia is assessed subjectively

Clinical features of leukoplakia

■ Homogeneous

- flat, uniform, predominantly white plaques
- may show shallow cracks/fissures

■ Non-homogeneous

- irregular nodular/thickened surface
- often speckled with areas of erythroplakia

■ Non-homogeneous lesions have a worse prognosis (more likely to be dysplastic, precancerous)

- **Erythroplakia:** a bright red velvety plaque on oral mucosa, homogeneous and well defined or intermingled with leukoplakia (erythroleukoplakia), may represent carcinoma *in situ*

Aetiological factors – multifactorial aetiology

- Tobacco
- Alcohol
- Candida (superimposed infection?)
- Viruses
- Oral epithelial atrophy (in iron deficiency, tertiary syphilis, submucous fibrosis, in vitamin deficiencies, sideropenic dysphagia)
- Inactivation of tumor suppressor genes

Epithelial dysplasia – reflects abnormalities in proliferation, maturation and differentiation of cells

- Increased and abnormal mitoses
- Basal cell hyperplasia
- Drop-shaped rete ridges (wider at their deepest part)
- Disturbed polarity of cells, loss of cellular orientation
- Increased N/C ratio
- Nuclear hyperchromatism
- Prominent and enlarged nucleoli
- Irregular epithelial stratification and disturbed maturation
- Nuclear and cellular pleomorphism
- Abnormal keratinization
- Loss or reduction of intercellular adhesion (or cohesion)

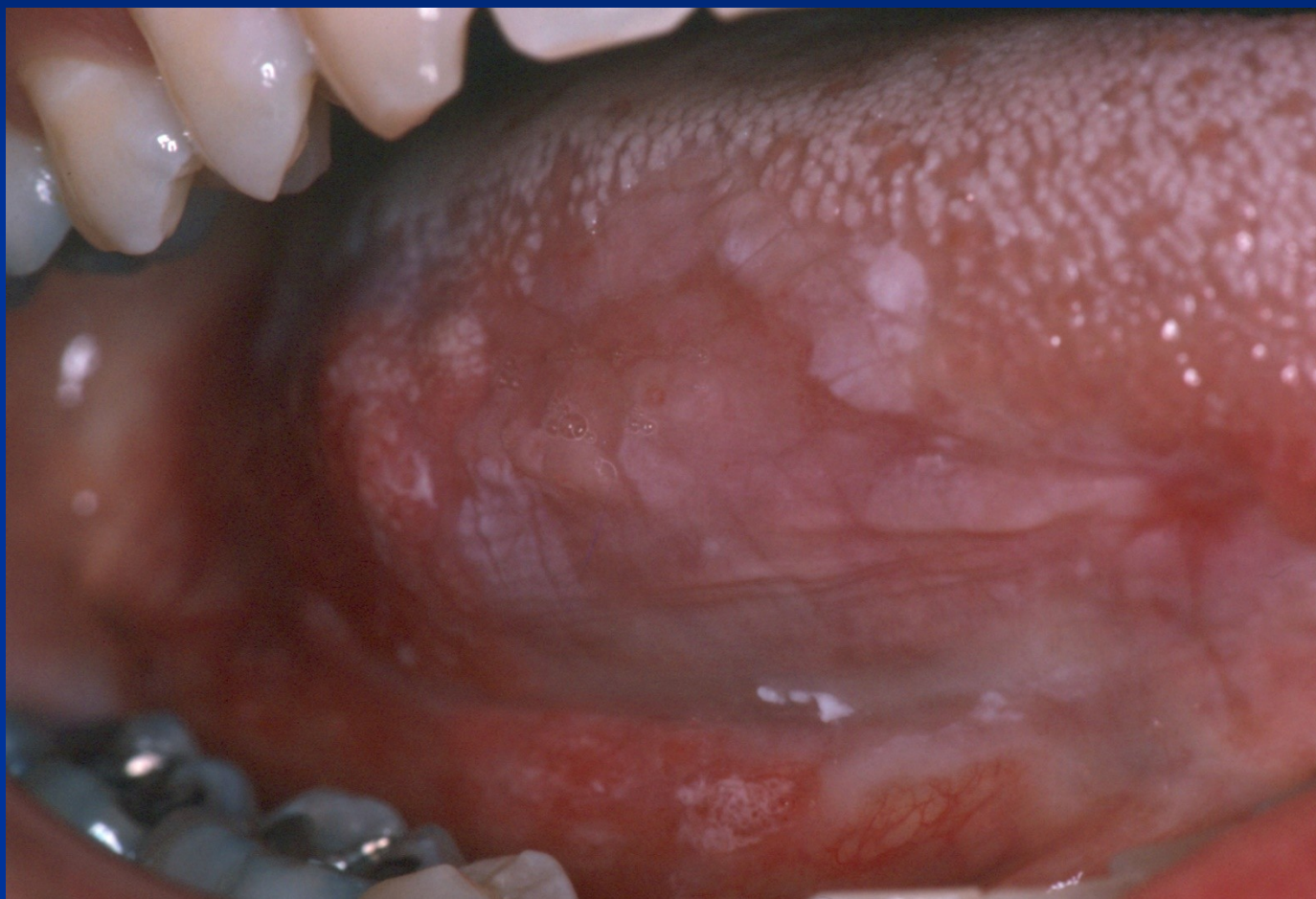
Prognosis of oral leukoplakia

- A proportion undergo malignant transformation
- Transformation times vary from one to several years
- Dysplastic lesions carry the risk of malignant transformation
- Malignant transformation likely to be due to progressive accumulation of genetic abnormalities over the time
- The potential for malignant transformation greater in high-risk sites (ventral tongue, floor of the mouth, lingual aspect of the lower alveolar mucosa)
- Lesions with abnormal DNA content (e.g. aneuploid – abnormal number of chromosomes) likely to progress to carcinoma

**Elevated keratotic lesion of lateral part of the tongue –
biopsy: focal benign keratosis.**



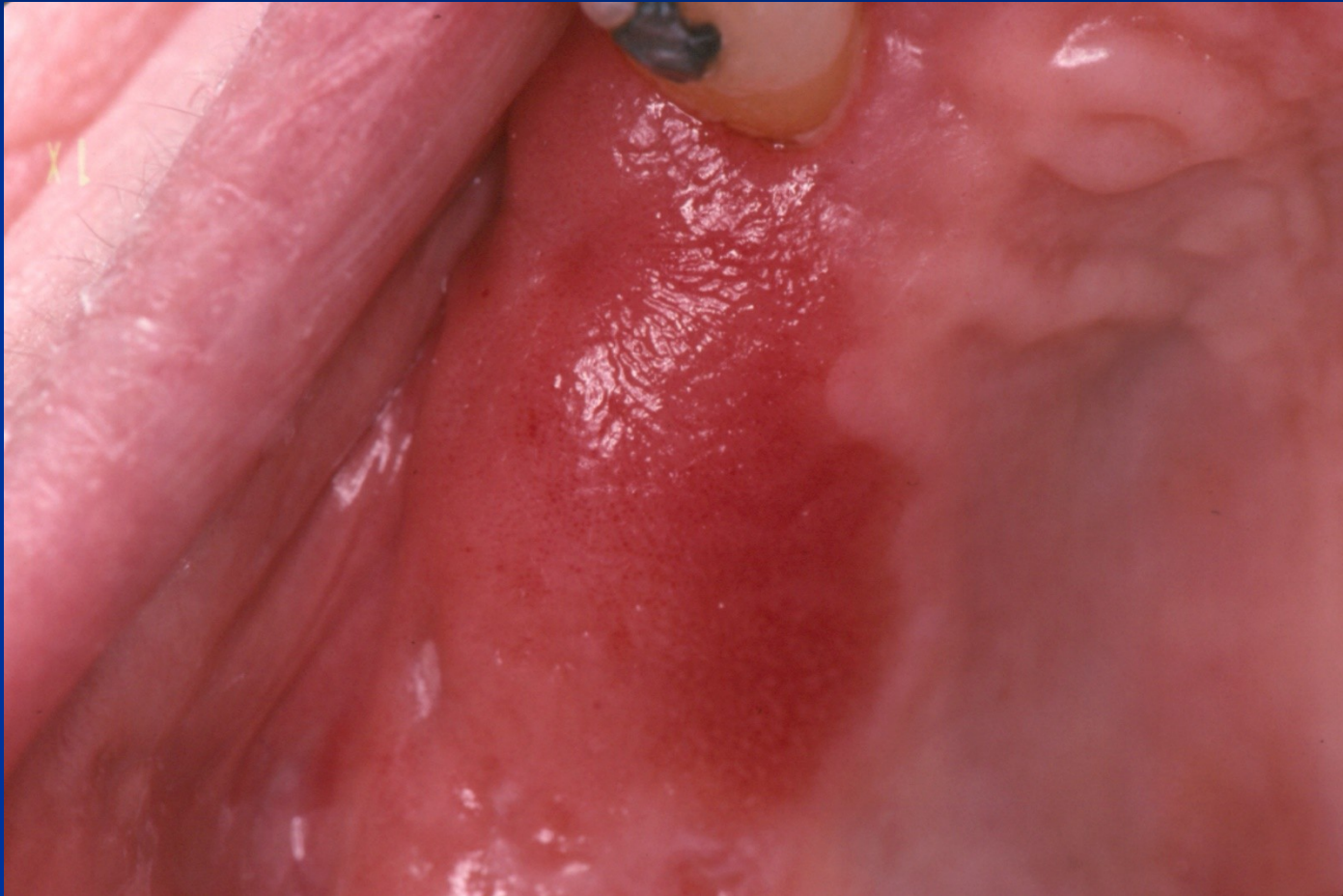
Patchy, focally thickened, keratotic lesions over the right lateral and ventral tongue surfaces – biopsy: focal moderate dysplasia



A mixed red and white lesion on the right ventral part of the tongue with atypical brush biopsy results and corresponding severe dysplasia by scalpel biopsy.



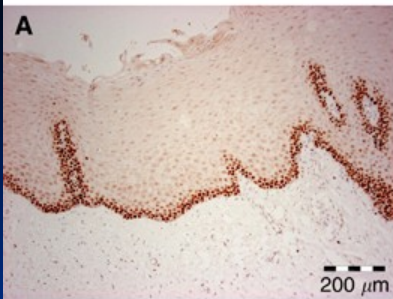
**Well-defined velvety patch of the maxillary alveolar ridge – biopsy:
carcinoma in situ.**



During a routine postradiation therapy examination, a focal red granular surface lesion was detected – biopsy: identification of recurrent invasive squamous cell carcinoma

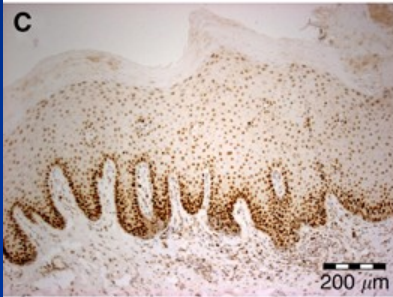
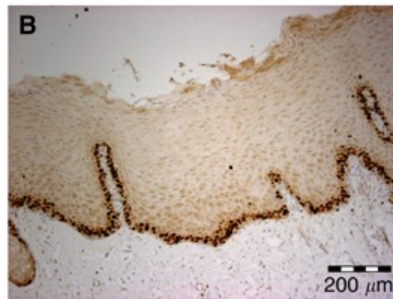


Mcm-2

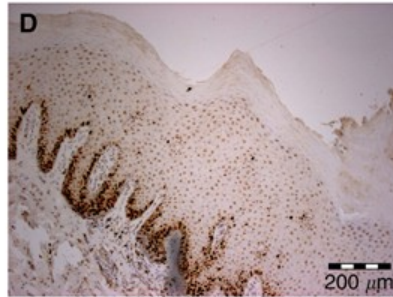


Oral keratosis

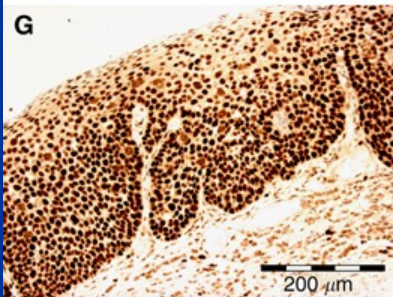
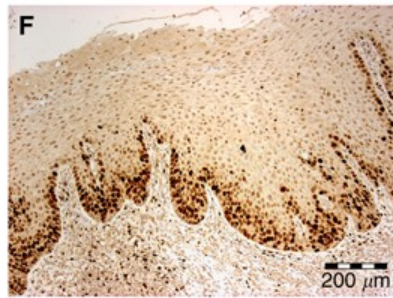
Ki67



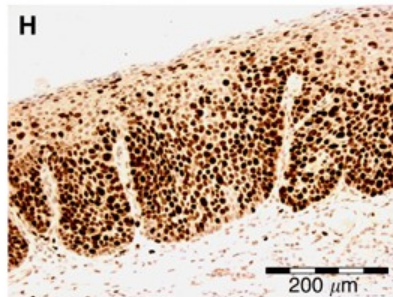
Mild dysplasia



Moderate dysplasia

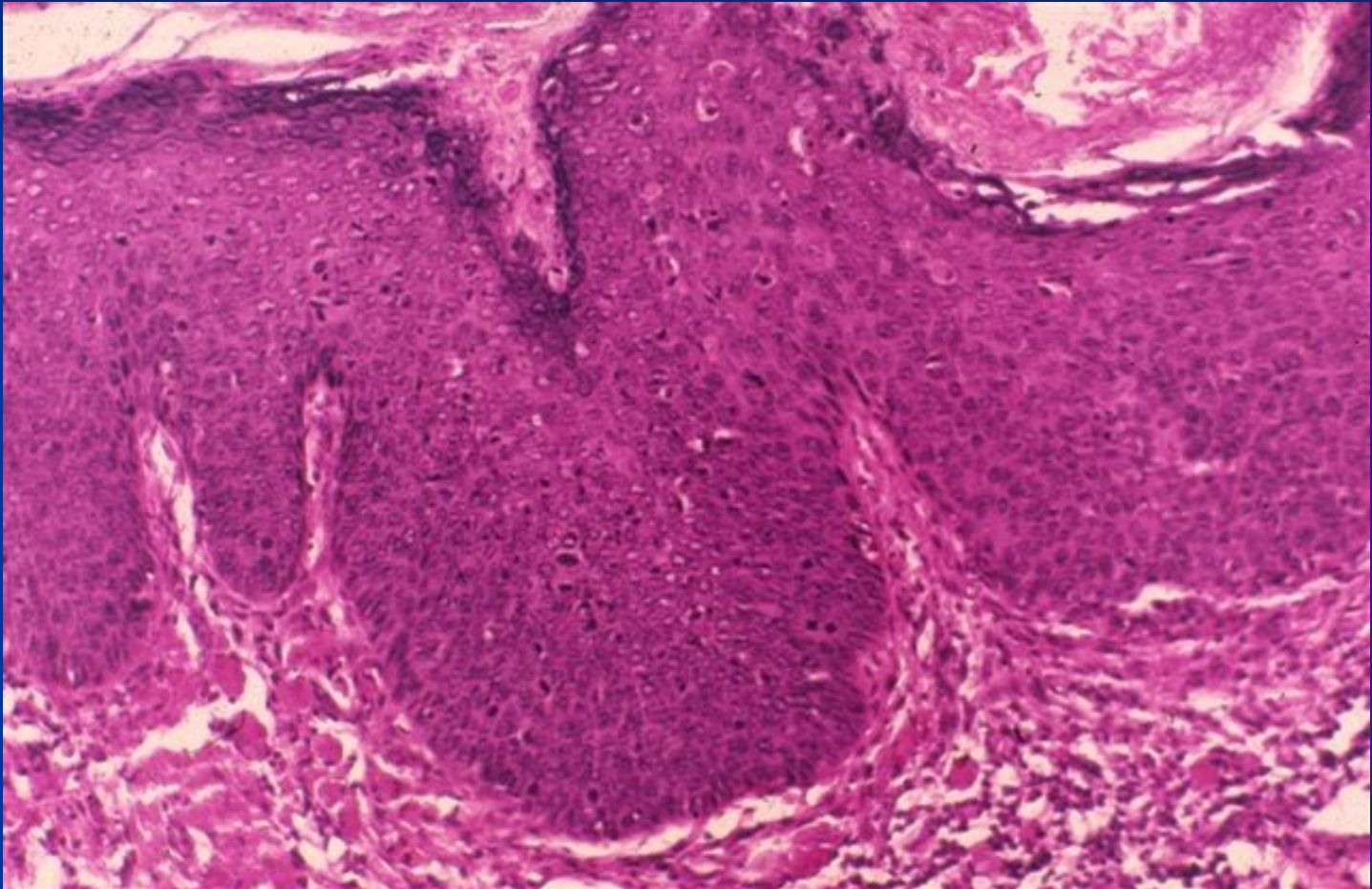


Severe dysplasia



Proliferative activity in benign and dysplastic oral lesions.

Carcinoma in situ



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

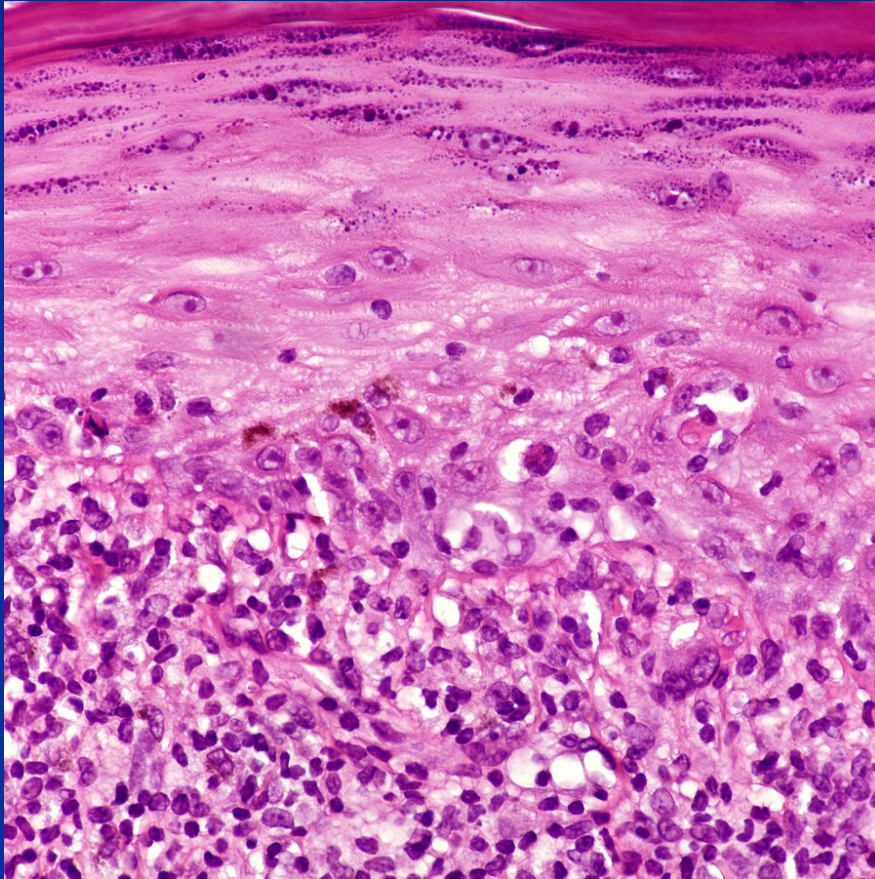
Clinical type of lichen planus

- 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



Lupus erythematosus (LE)

■ **Chronic discoid LE (localized LE)**

- Facial skin may be involved (butterfly pattern)
- Cheeks commonest oral site
- Discoid area of erythema with keratotic borders

■ **Systemic LE (disseminated disease)**

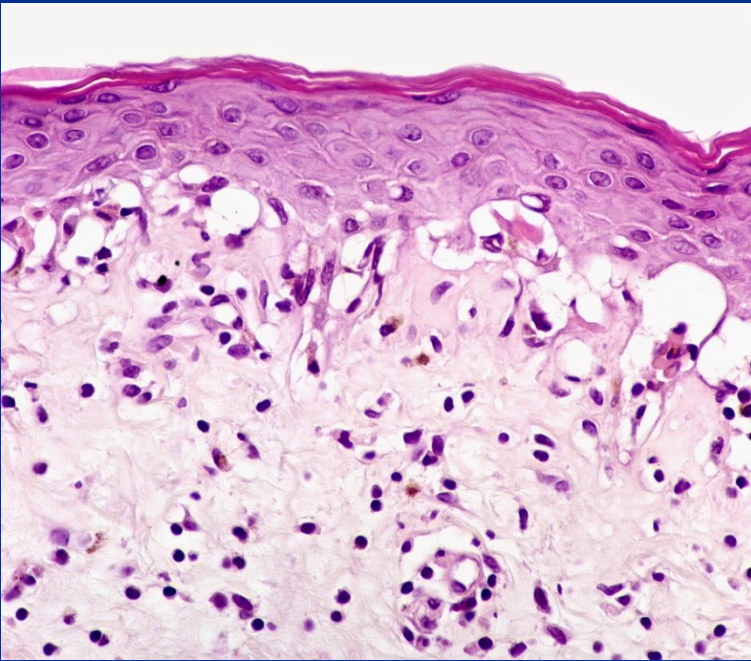
- Skin rashes and systemic involvement
- Oral lesion variable

■ **F>M**

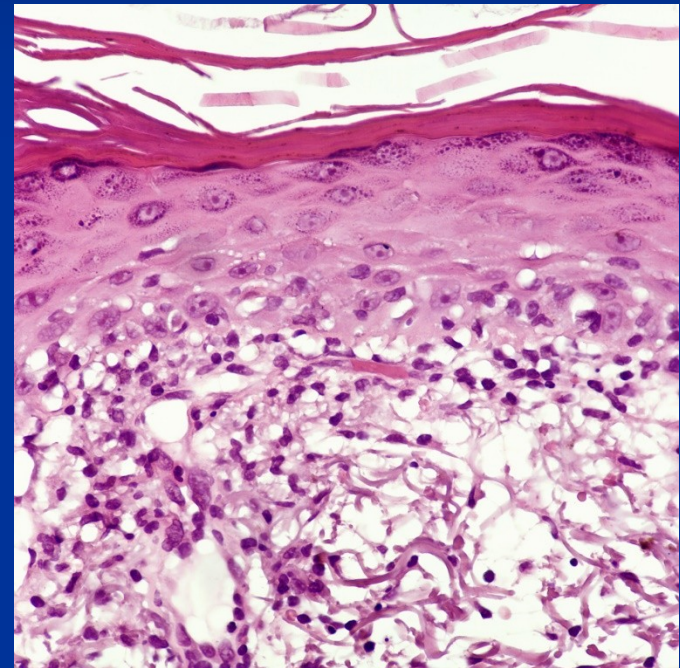
■ **Autoimmune disease** (a variety of autoantibodies (ANA))

- **Histology** of oral lesion often nonspecific (lymphocytic infiltration – perivascular, in connective tissue, may be liquefactive degeneration of basal cells; abundant deposits of Ig (IgG) and complement in the basement membrane zone forming a prominent „lupus band“

Lupus erythematosus (LE)

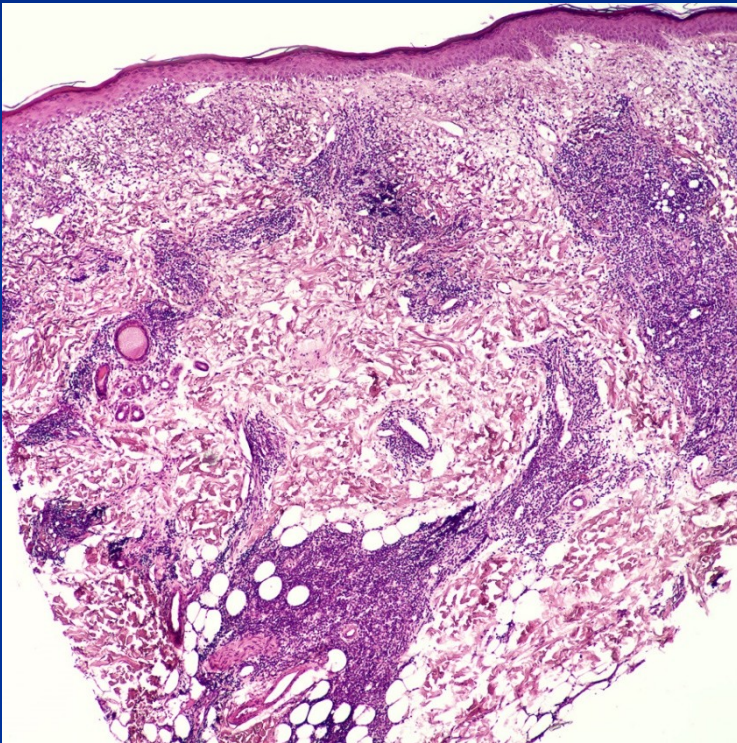


Lupus erythematosus subacutus

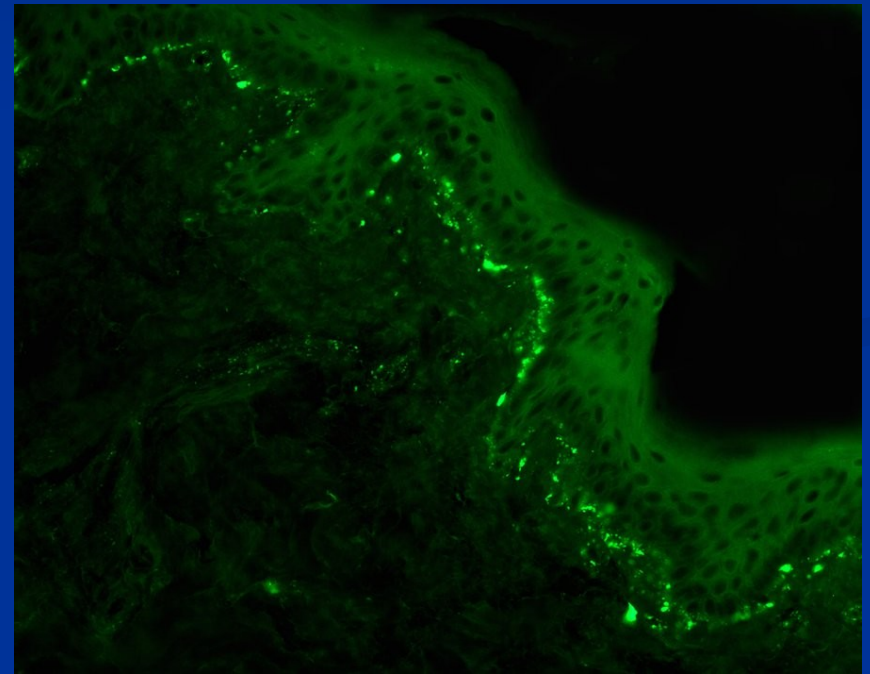


Lupus erythematosus chronicus

Lupus erythematosus (LE)



Lupus erythematosus chronicus



Direct immunofluorescence: granular deposits subepidermally

Epidermolysis bullosa

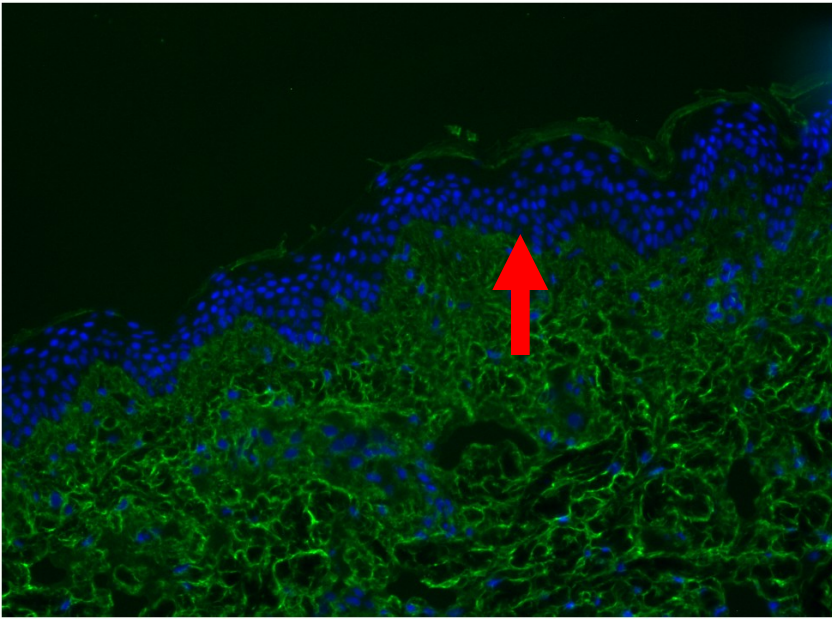
- Inherited disease, 30 types
- Mutations in genes coding specific keratins in the basal epithelial layer (intraepithelial bullae), collagens and other attachment proteins (subepithelial bullae)
- Extreme fragility of the skin
- Mucosae also affected

EB type	EB subtype	Involved genes
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	$\alpha 6\beta 4$ integrin
DEB	DDEB	collagen VII
	RDBE, Hallopeau-Siemens	collagen VII
	RDEB, non- Hallopeau-Siemens	collagen VII

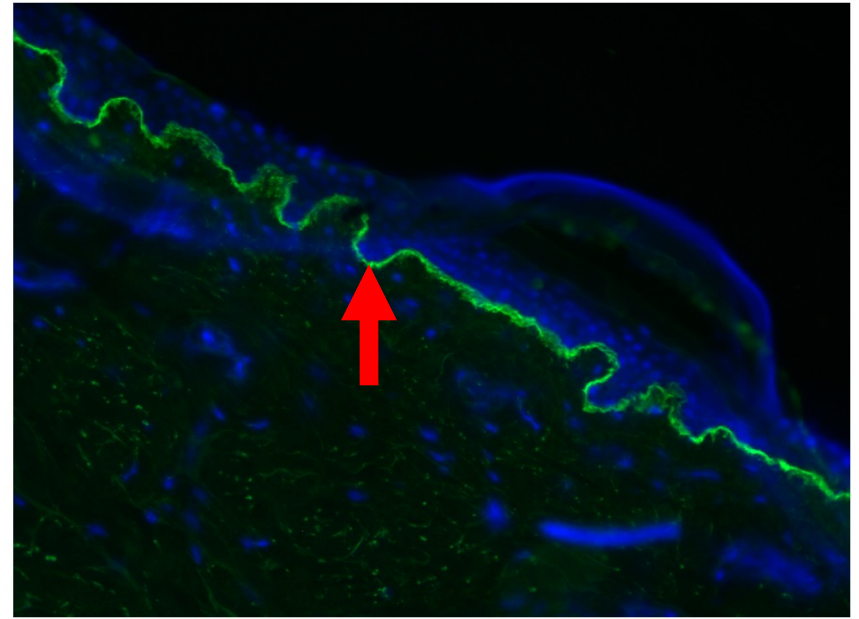
EBS, epidermolysis bullosa simplex
JEB, junctional epidermolysis bullosa

DDEB, dominant dystrophic epidermolysis bullosa
RDEB, recessive dystrophic epidermolysis bullosa

Epidermolysis bullosa: immunofluorescence

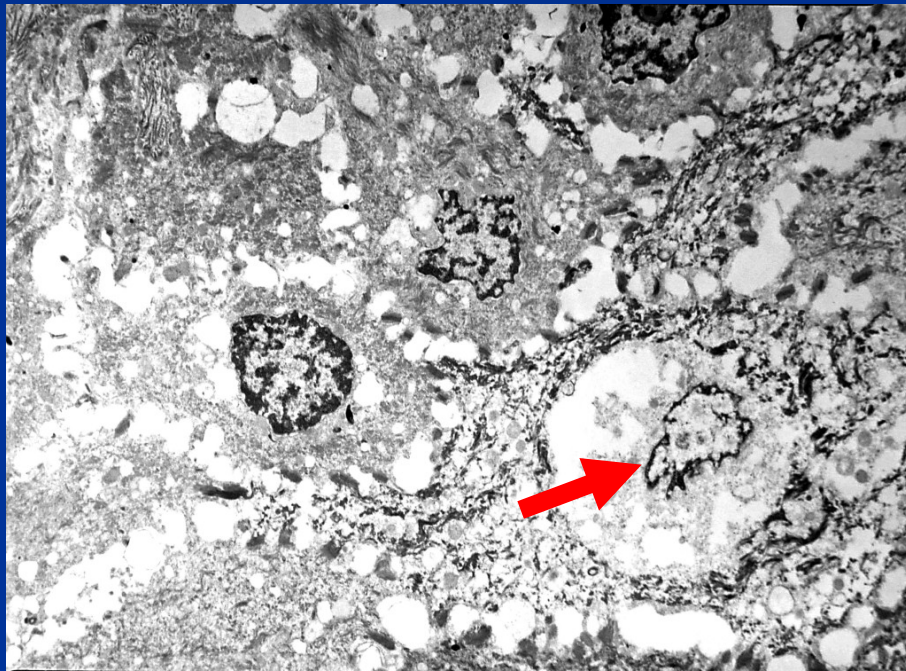


Absence of collagen VII in DE junction

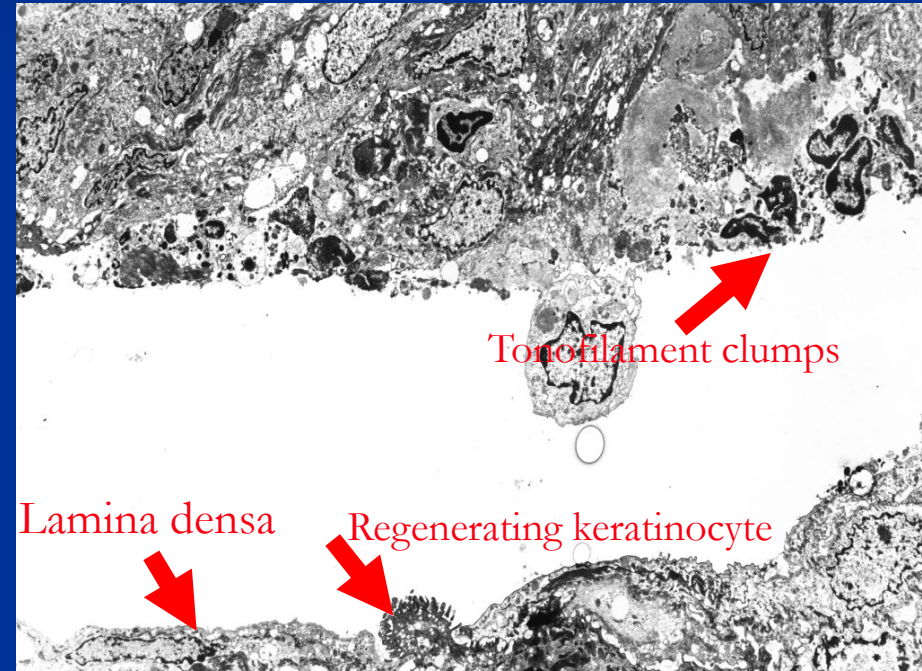


Normal control with presence of collagen VII

Epidermolysis bullosa: ultrastructural examination

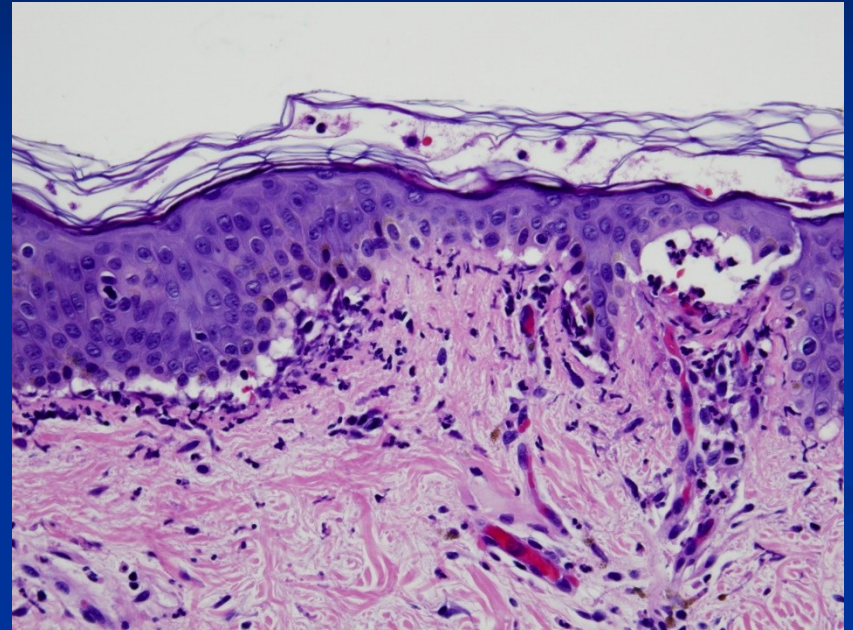


Lysis of keratinocytes in EB dystrophica



EB simplex

Epidermolysis bullosa acquisita



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

