Keratoses and precancerous and premalignant lesions and conditions.

Markéta Hermanová

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:
premalignant 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/intraepitelial 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

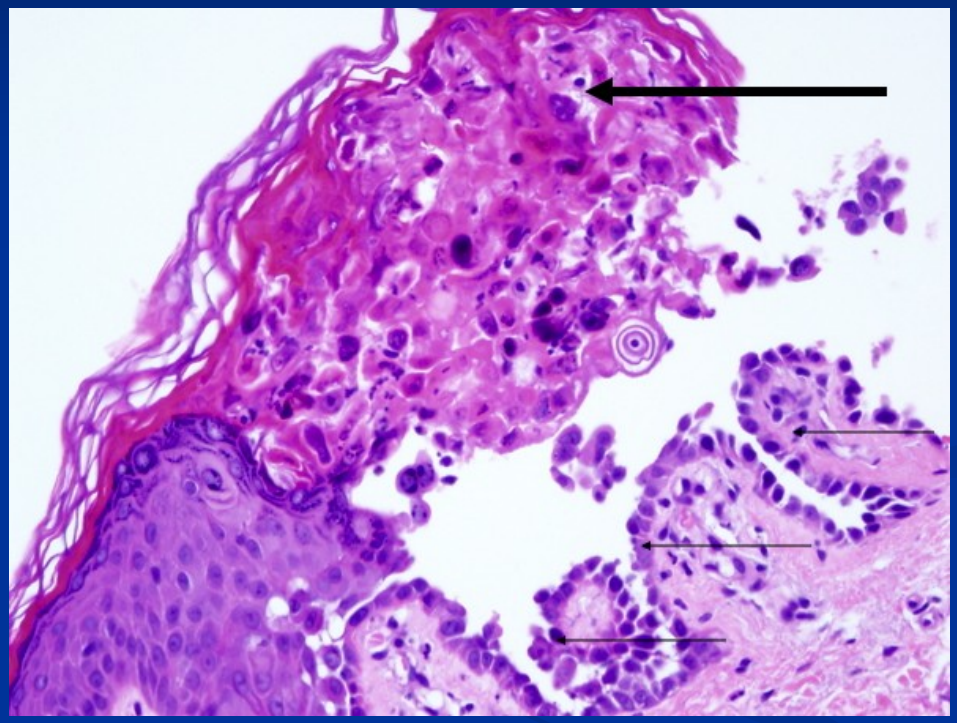
- **Neoplastic**
  - Carcinoma *in situ*
  - SCC

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 cannto be characterized clinically or histopathologically as any ather 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 erytroplakia

- **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 intermigled 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 deficiences, sideropenic dysphagia)
- Inactivation of tumor suppressor genes

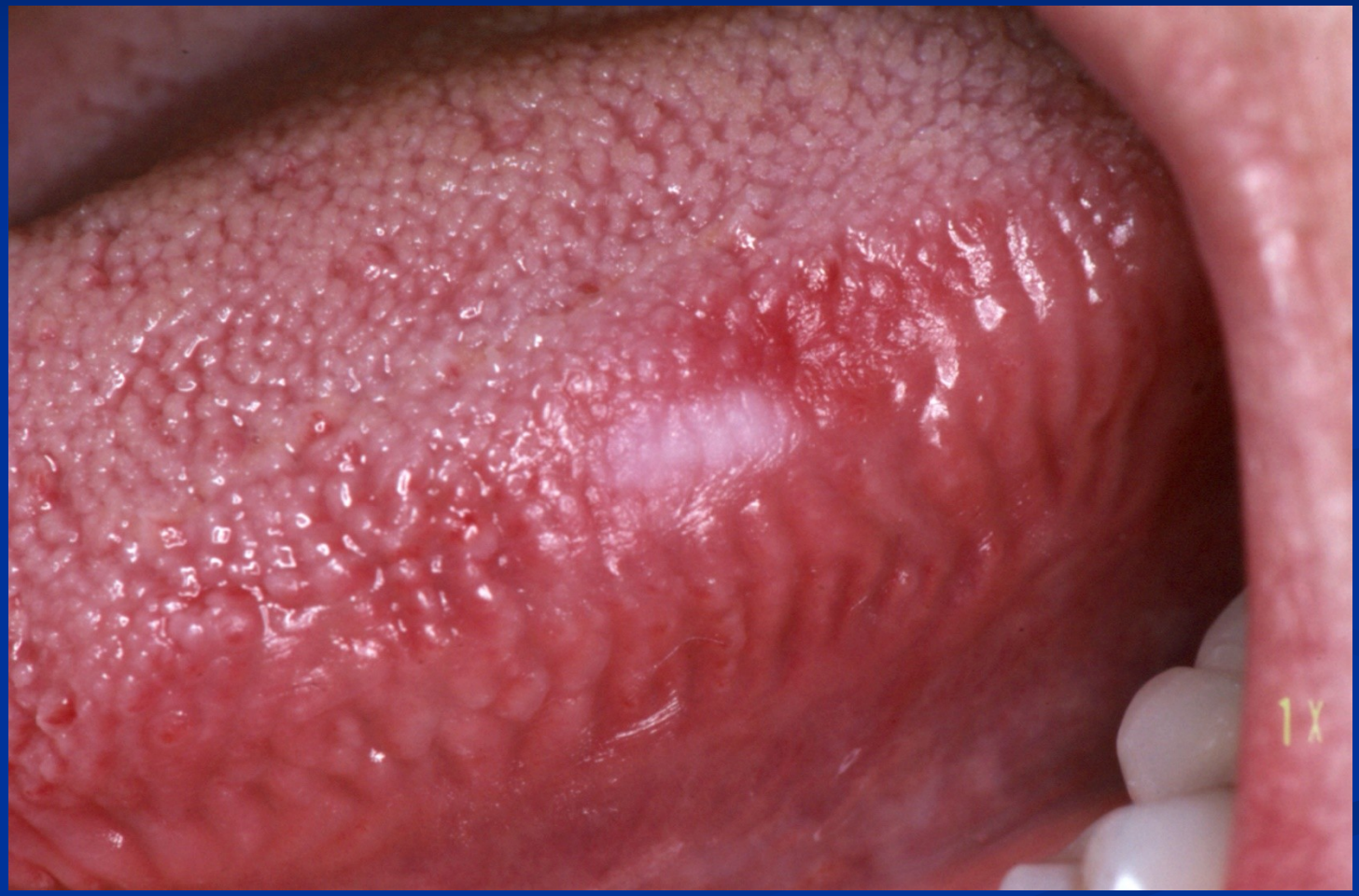
Epithelial dysplasia – reflects abnormalities in proliferation, maturation and differentiation of cells

- Increased and abnormal mitoses
- Basal cell hyperplasia
- Drop-shaped rete ridges (wider at their deepest part)
- Disturbed polarity of cells, losss of cellular orientation
- Increased N/C ration
- 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)

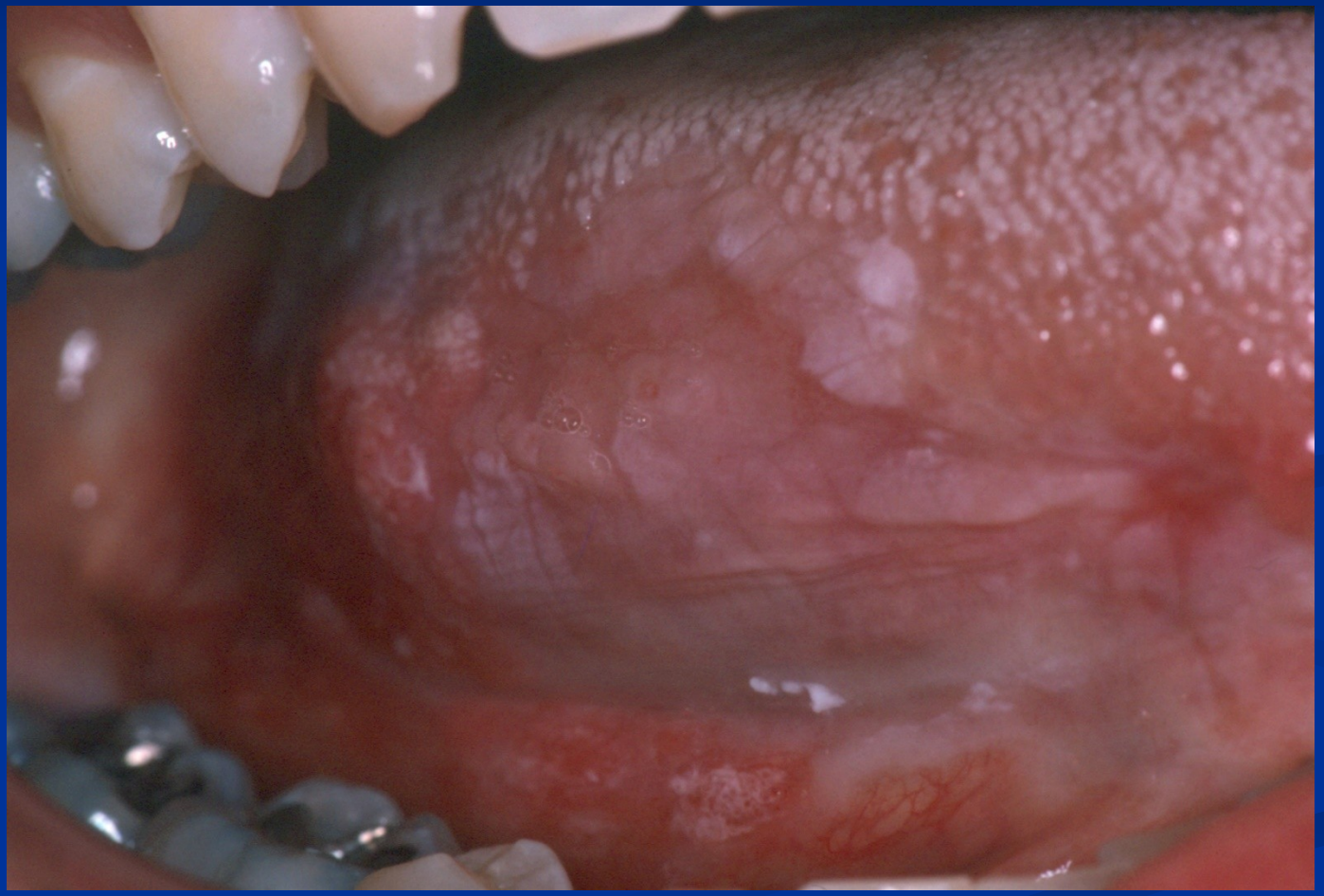
Prognosis of oral leukoplakia

- A proportion undergo malignant transformation
- Transformation times vary from one to several years
- Dysplastic lesions carry the risk of malignant tranformation
- Malignant transformation likely to be due to progressive accumulation of genetic abnormalities over the time
- The potential for malignant tranformation 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

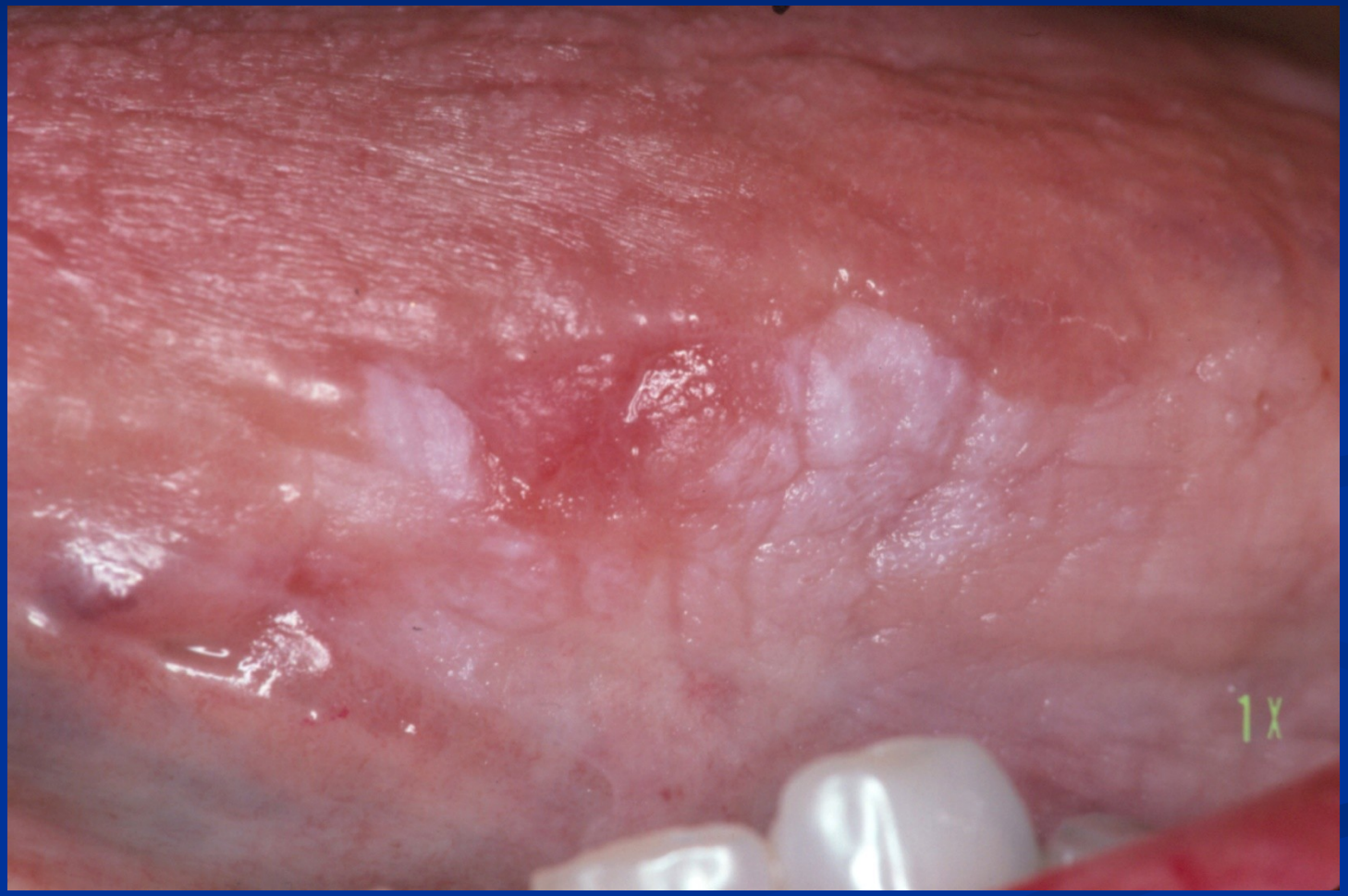
Elevated keratotic lesion of lateral part of the tongue – biopsy: focal benign keratosis.



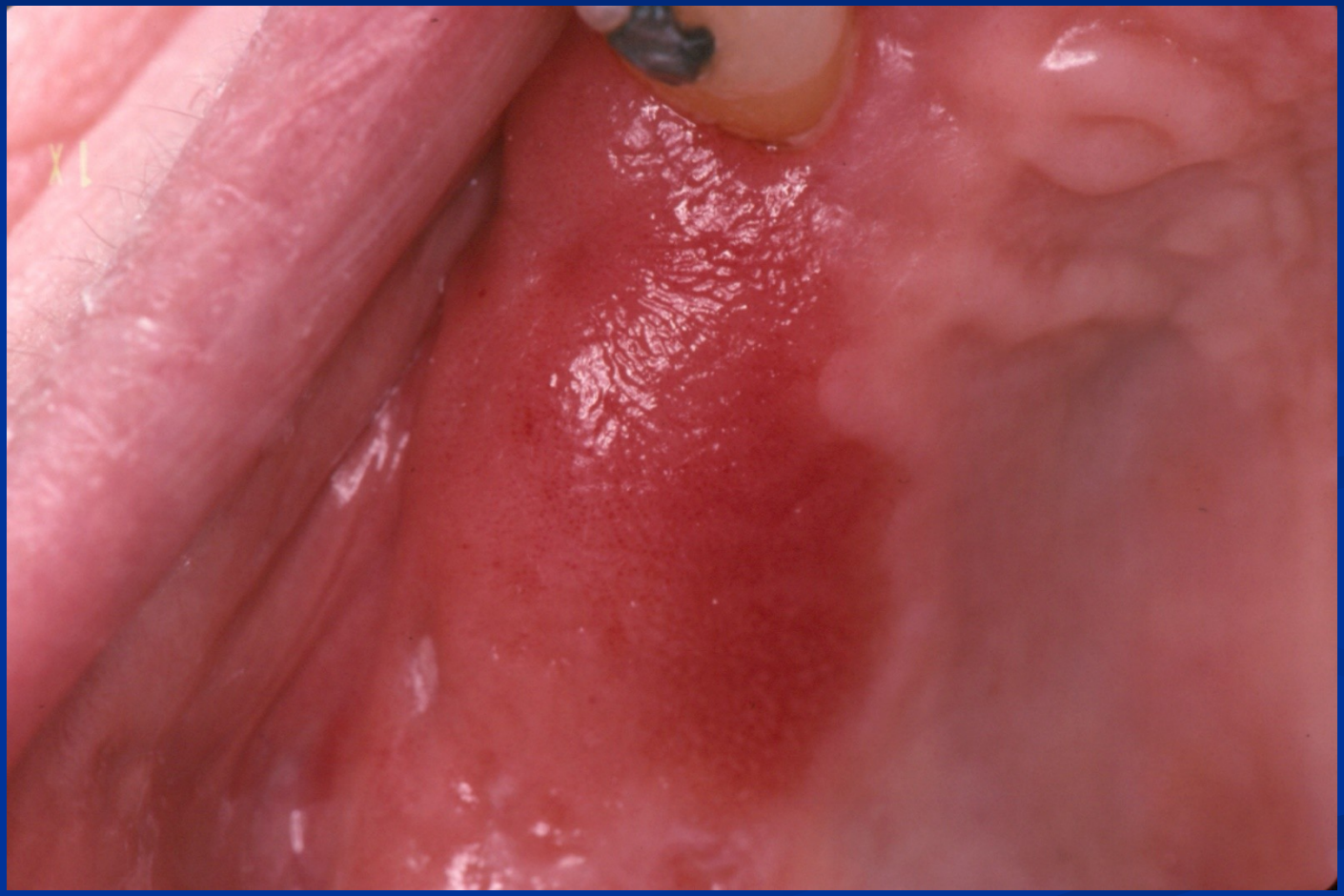
Patchy, focally thickened, keratotic lesions over the right lateral and ventral tongue surfaces – biopsy: focal moderate dysplasia



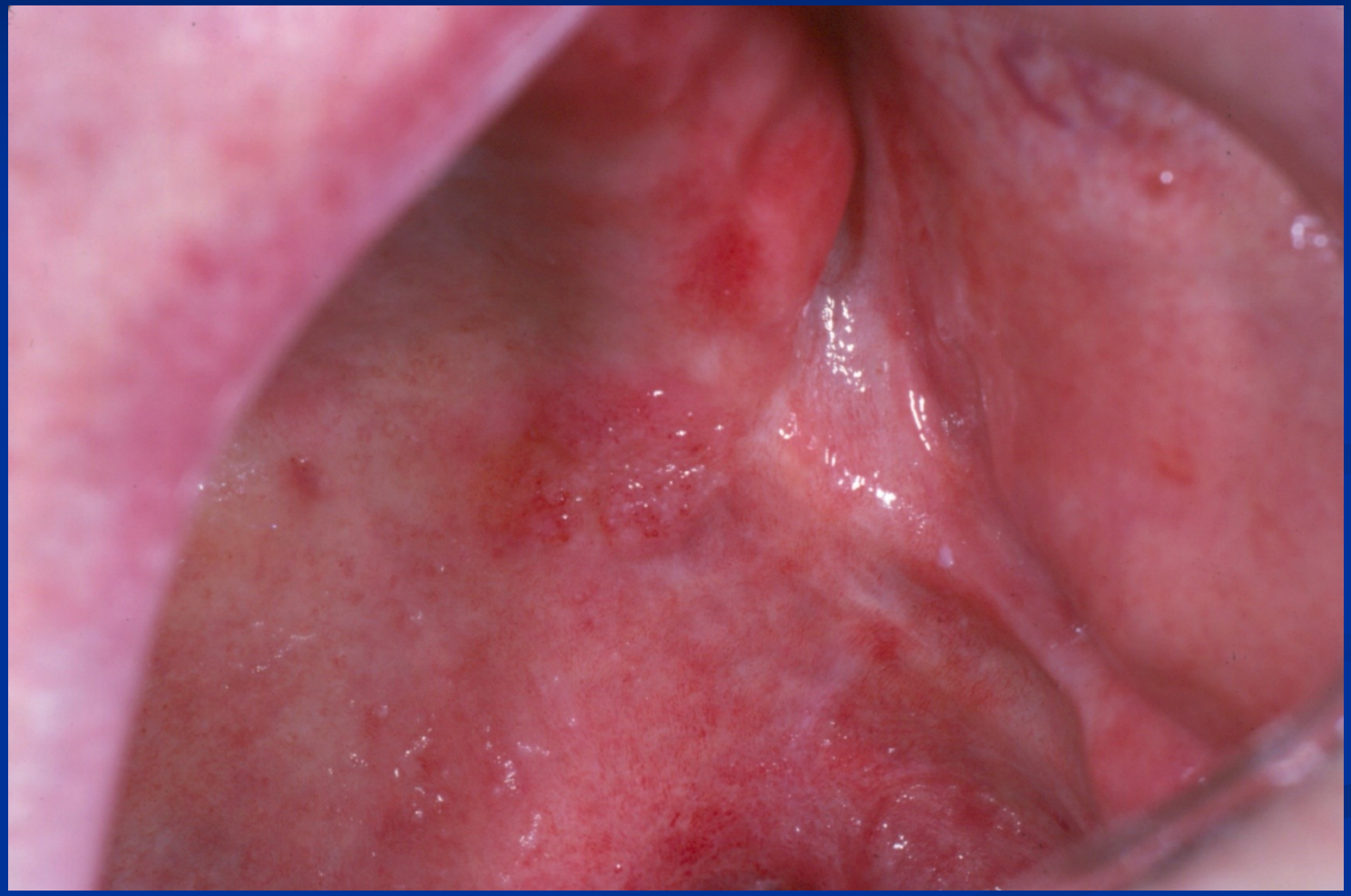
A mixed red and white lesion on the right ventral part of the tongue with atypical brush biopsy results and corresponding severe dysplasia by scalpel biopsy.

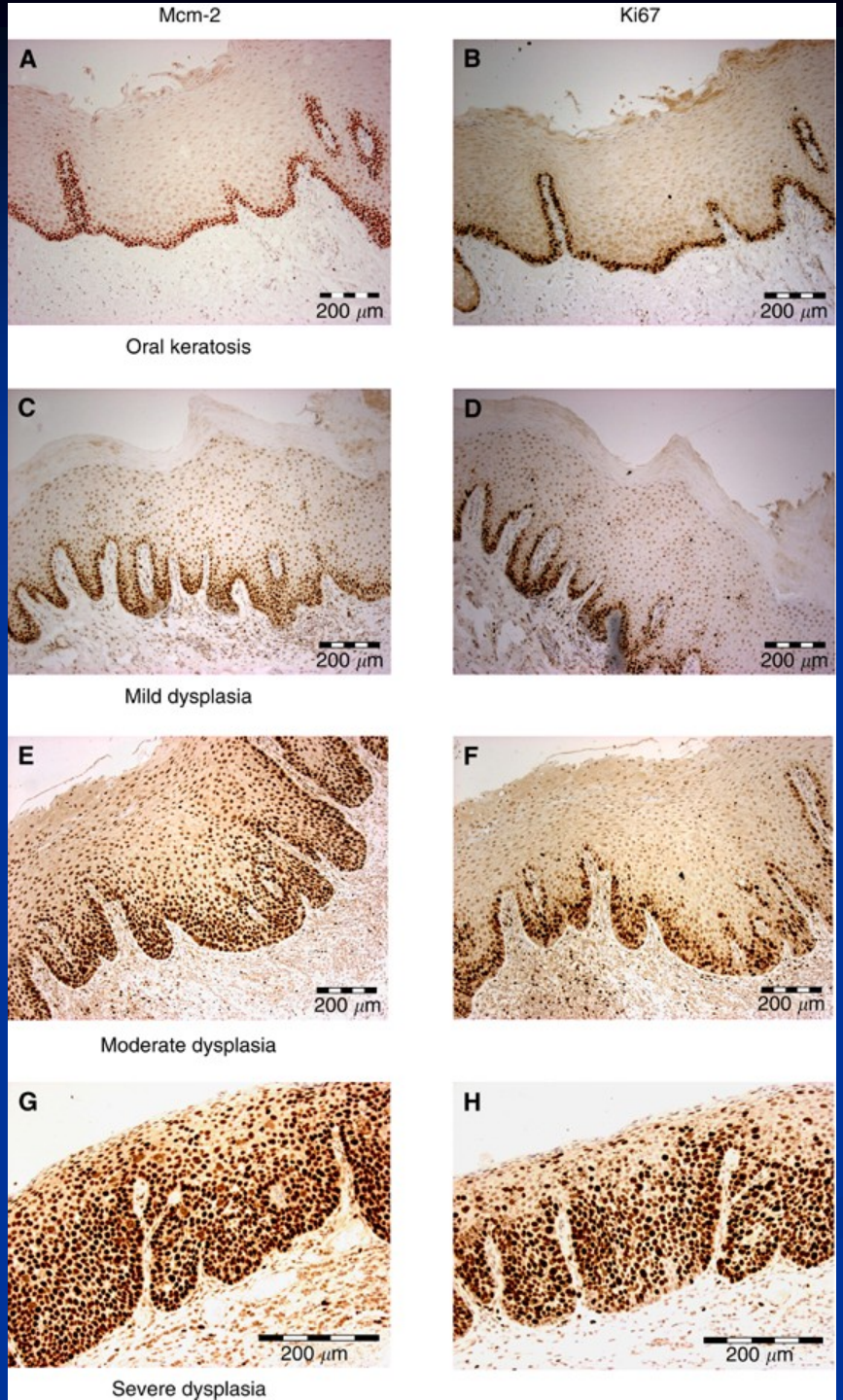


Well-defined velvety patch of the maxillary alveolar ridge – biopsy: carcinoma in situ.



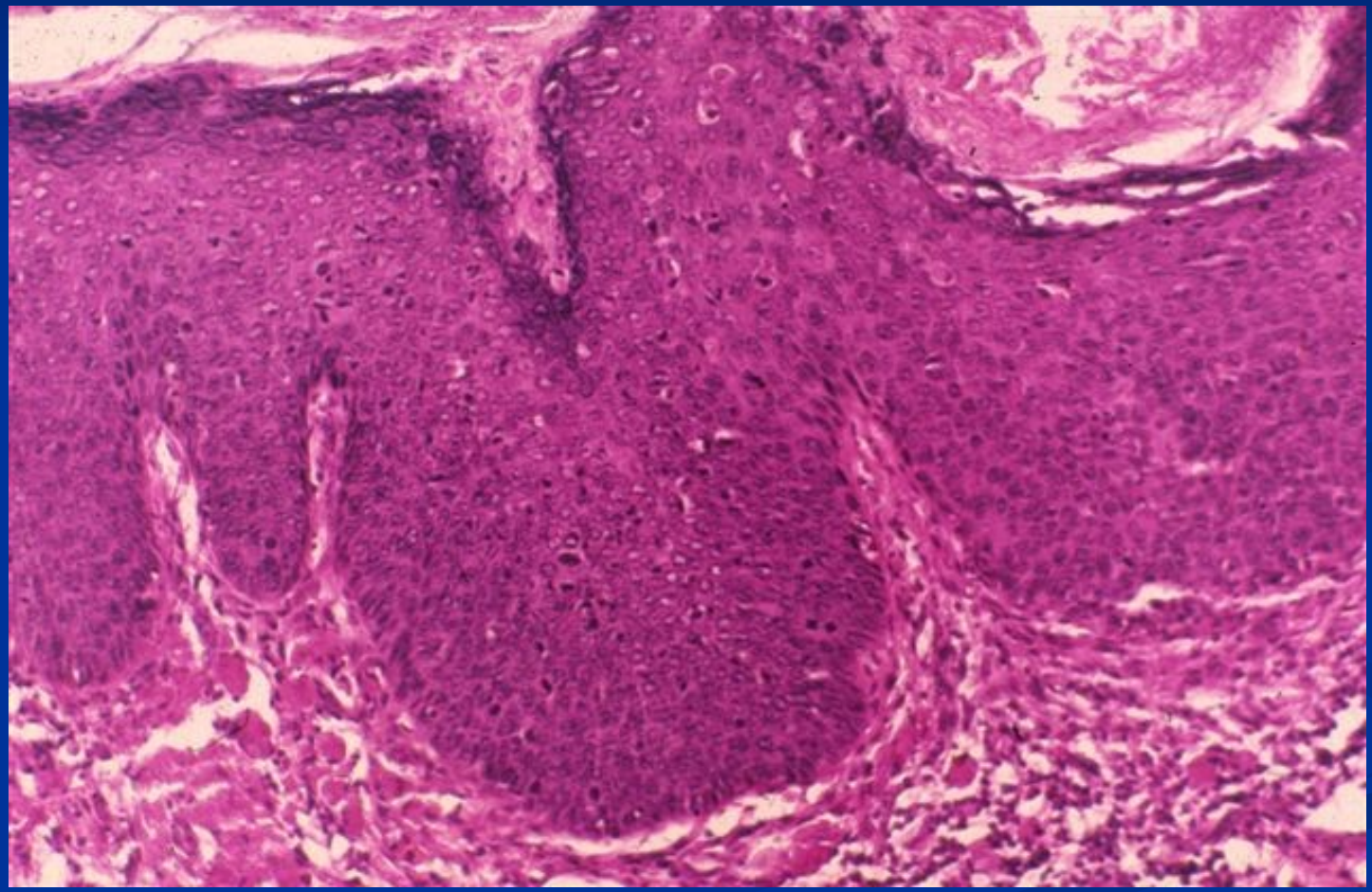
During a routine postradiation therapy examination, a focal red granular surface lesion was detected – biopsy: identification of recurrent invasive squamous cell carcinoma





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

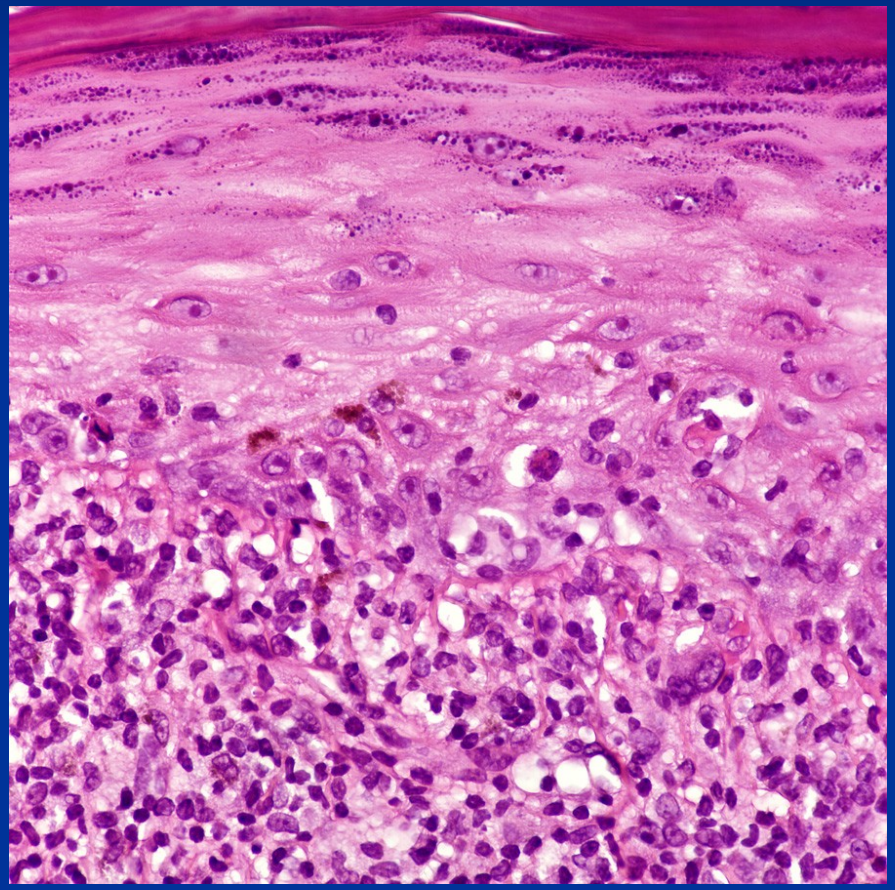
Clinical type of lichen planus

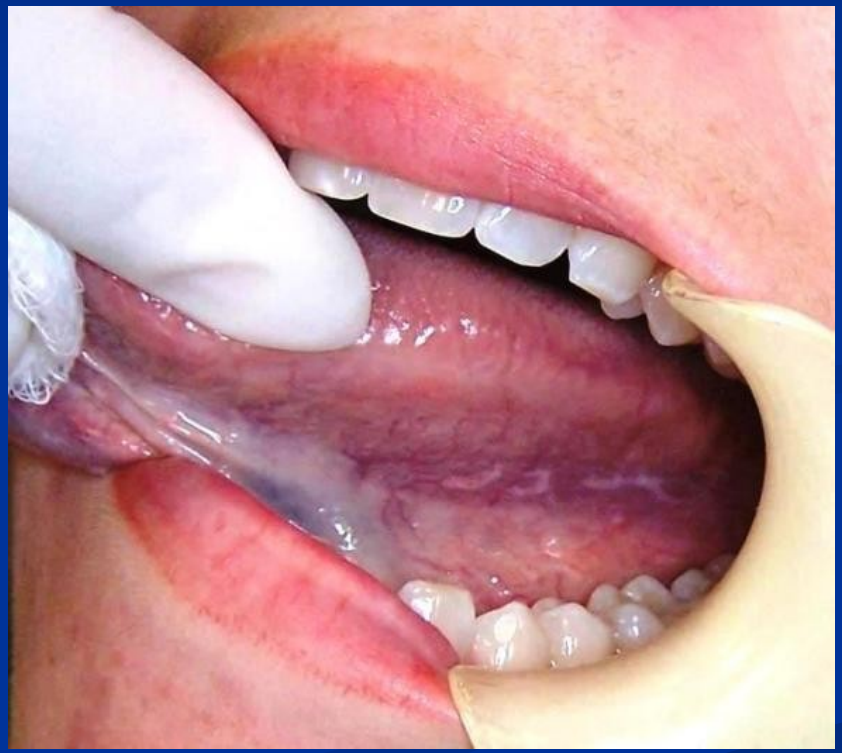
- Reticular (lace-like striae)
- Atrophic (resemble erythroplakia)
- Plaque-like (resemble leukoplakia)
- Papular
- Erosive
- Bullous

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

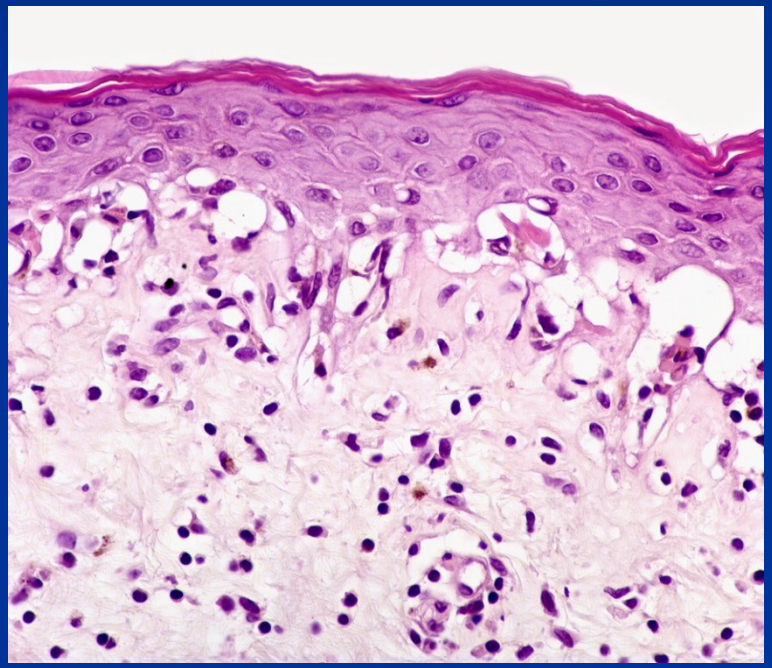




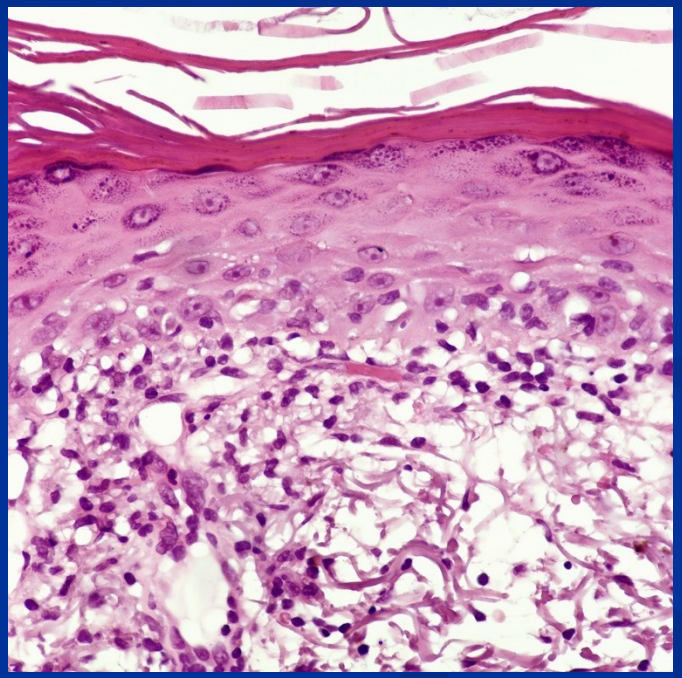
Lupus erythematosus (LE)

- **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)

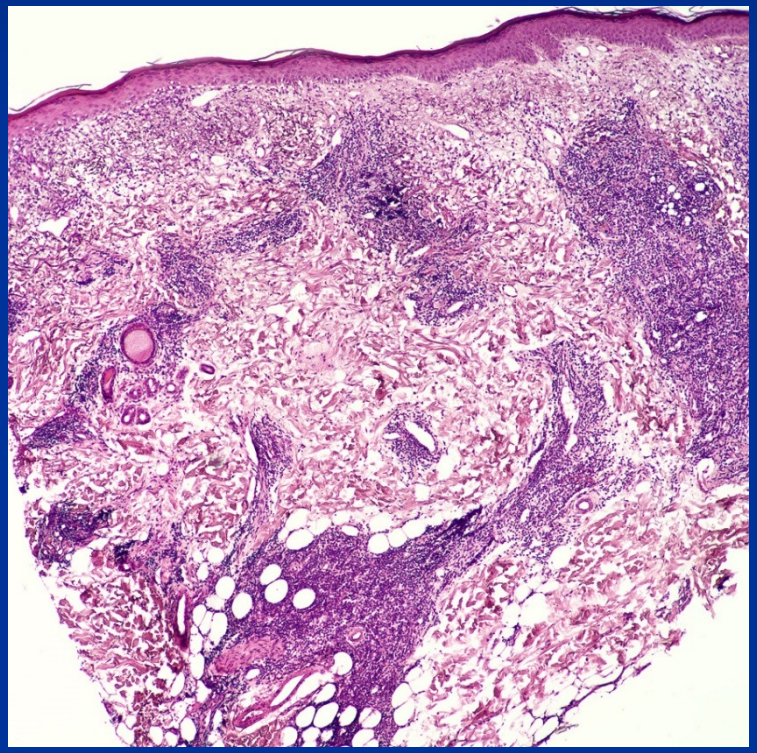


Lupus erythematosus subacutus

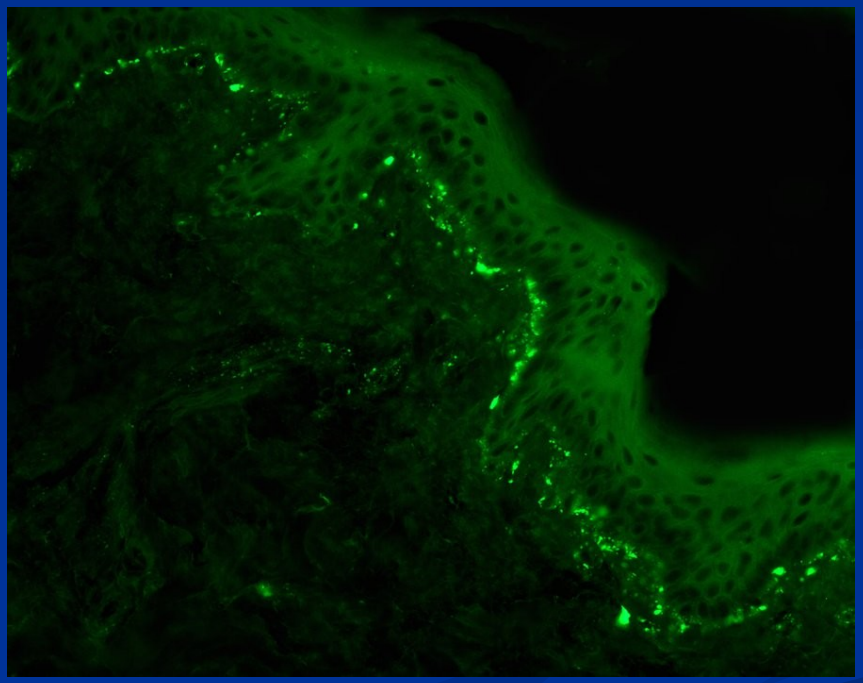


Lupus erythematosus chronicus

Lupus erythematosus (LE)



Lupus erythematosus chronicus



Direct immunofluorescence: granular deposits subepidermally

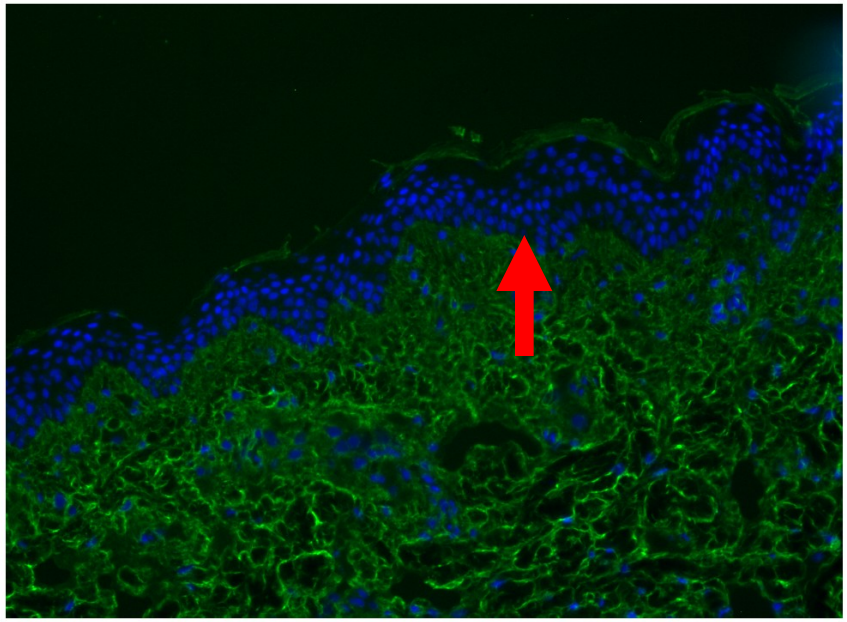
Epidermolysis bullosa

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

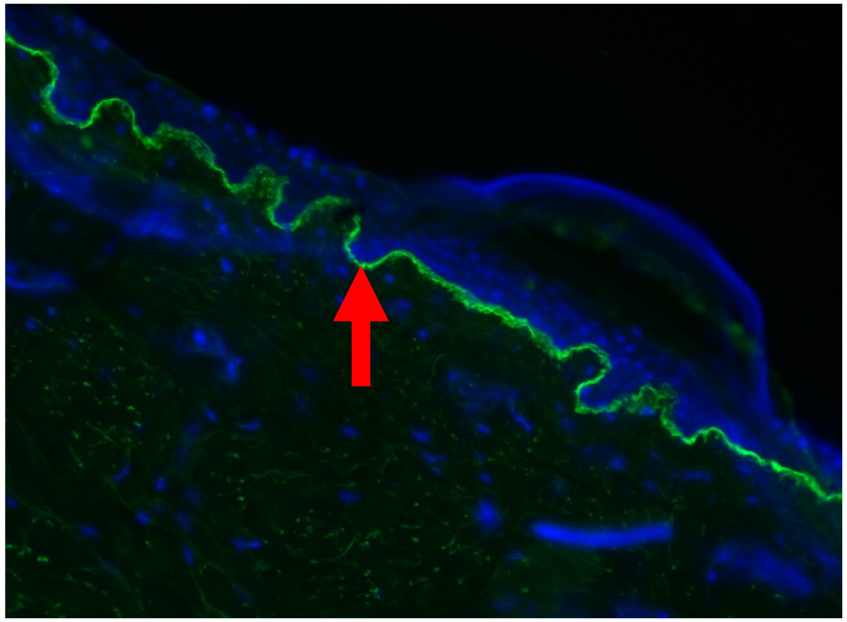
EB type	EB subtype	Involved genes
EBS	EBS, Weber-Cockayne	K5, K14
	EBS, Koebner	K5, K14
	EBS, Dowling-Meara	K5, K14
	EBS with muscular dystrophy	plectin
JEB	JEB, Herlitz	laminin 5
	JEB, non-Herlitz	laminin 5, collagen XVII
	JEB with pyloric atresia	α6β4 integrin
DEB	DDEB	collagen VII
	RDBE, Hallopeau-Siemens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

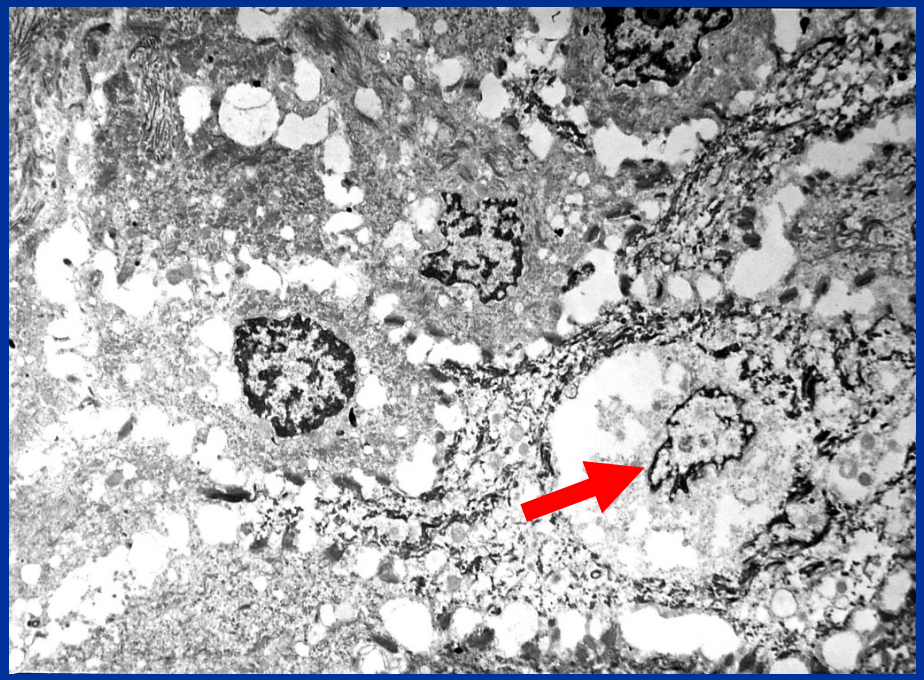


Absence of collagen VII in DE junction

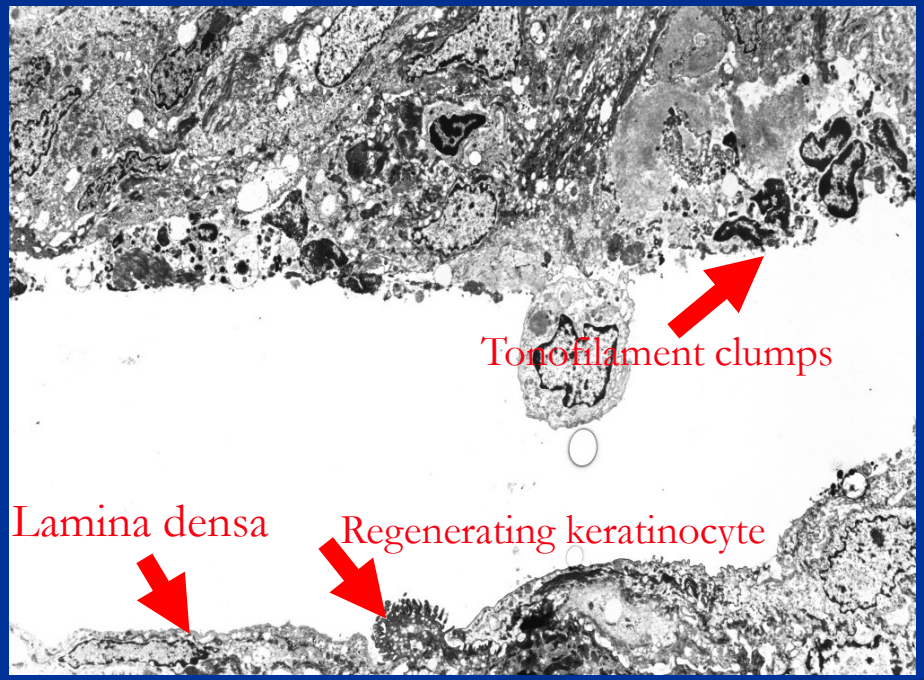


Normal control with presence of collagen VII

Epidermolysis bullosa: ultrastructural examination

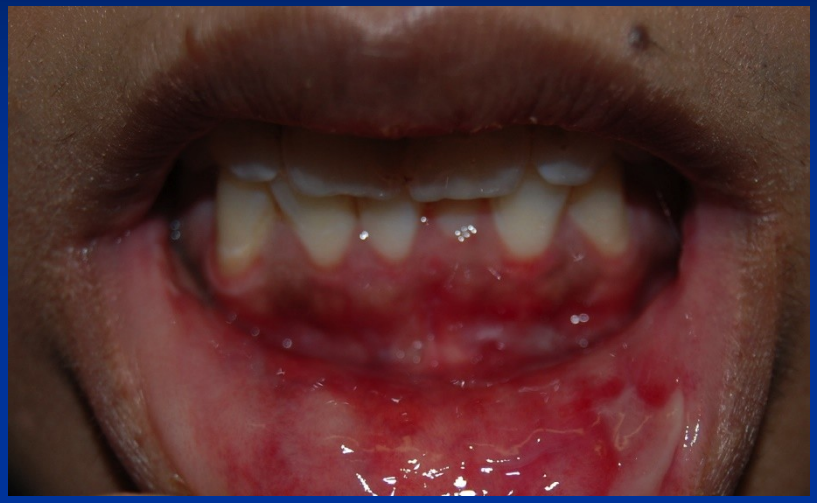


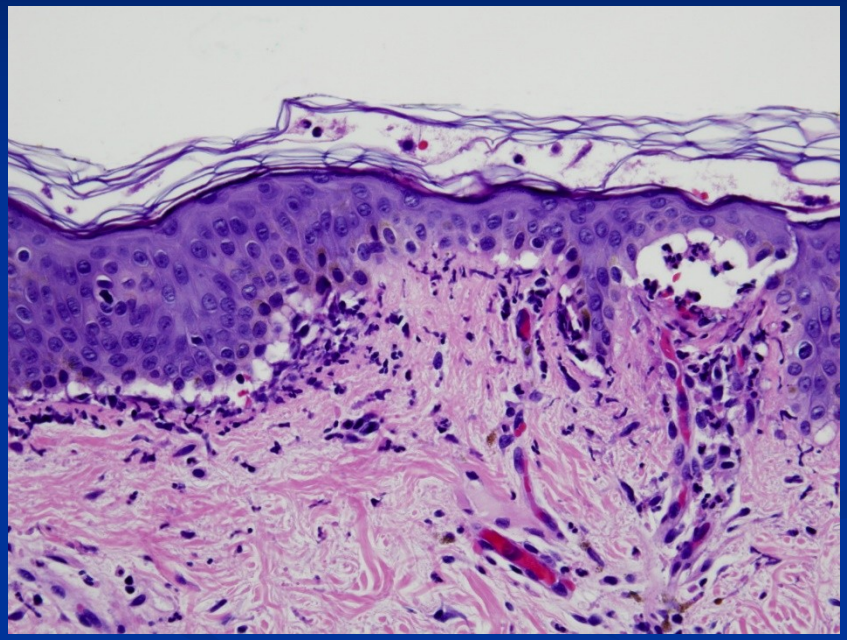
Lysis of keratinocytes in EB dystrophica



EB simplex

Epidermolysis bullosa acquisita





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

Thank you for your attention …