Vesicullo-Bullous Disorders

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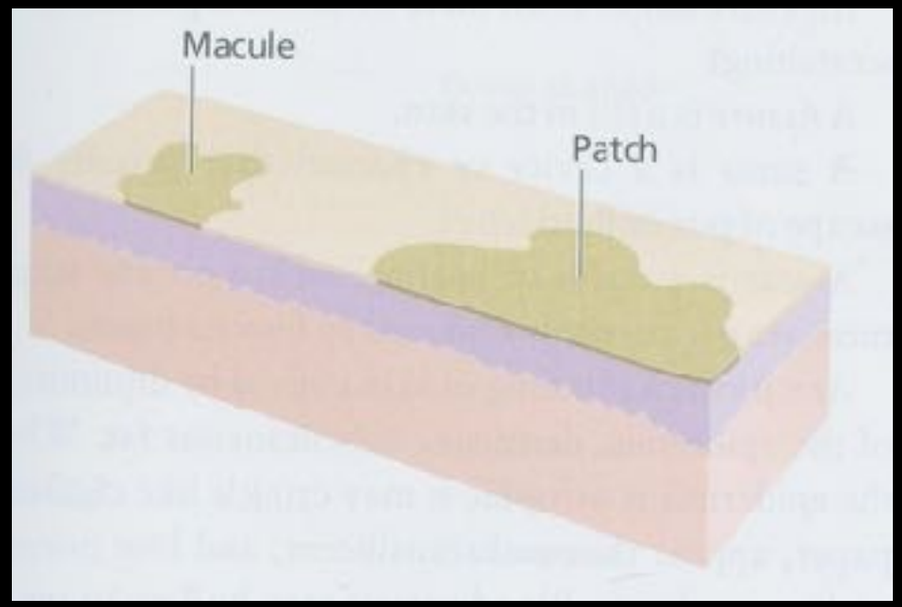
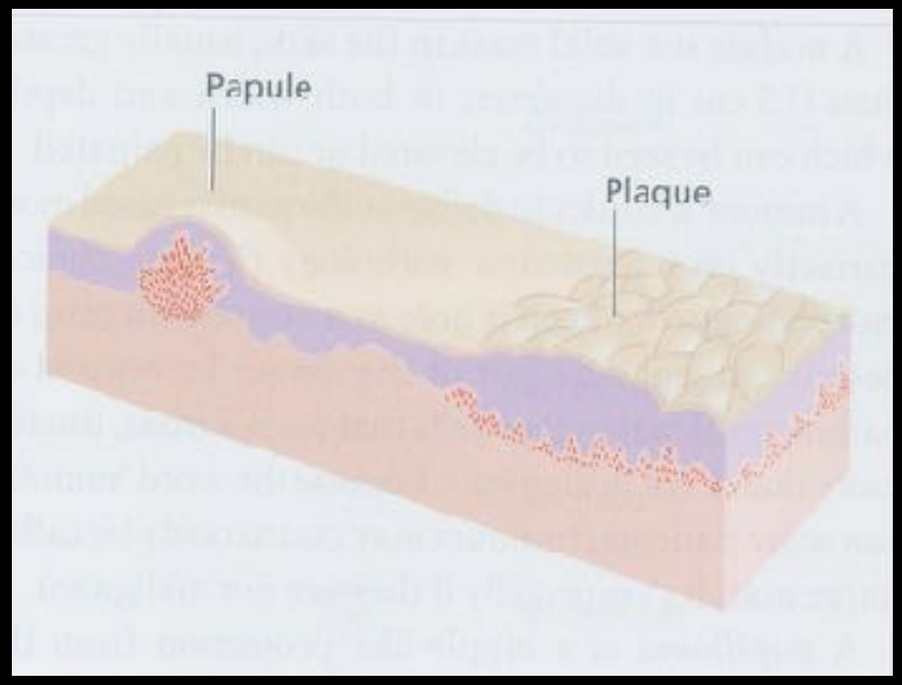
3rd Oct 2019

6th Oct 2019



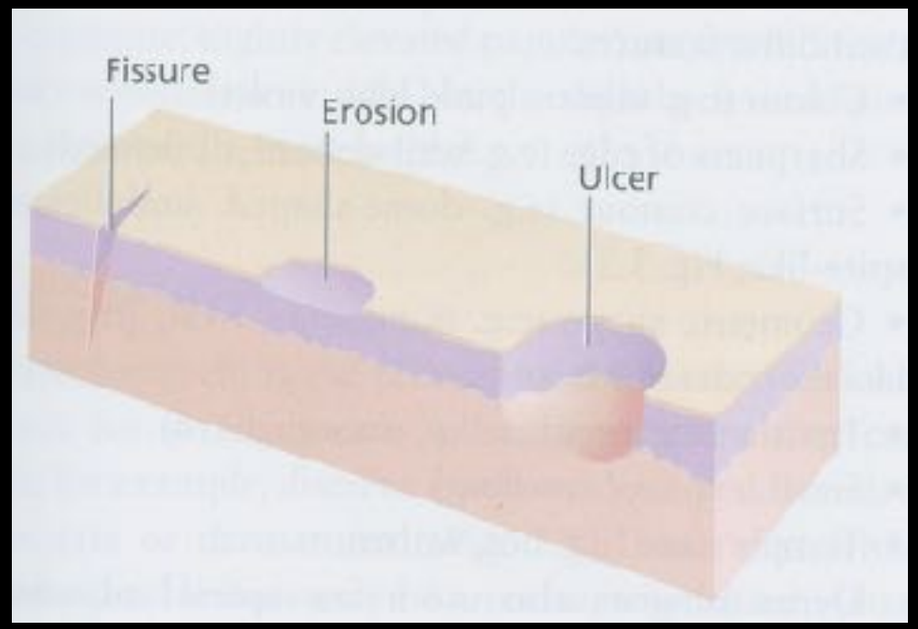
Macules: small flat area of altered colour or texture

Patch: large flat area of altered colour or texture



Papule: solid and raised lesion smaller than 1 cm

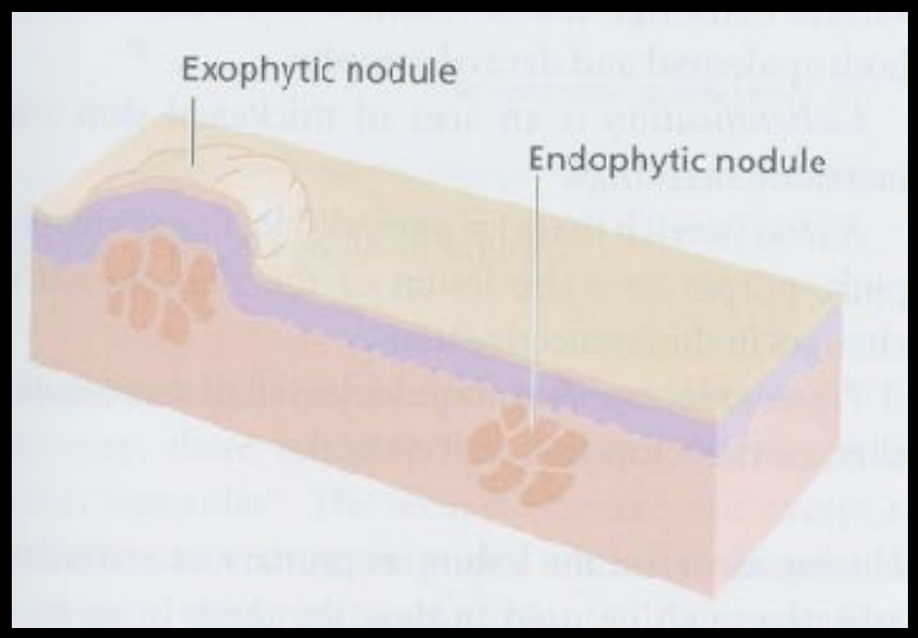
Plaque: solid and raised lesion larger than 1 cm (large papules)



Fissure: linear cut in the epithelium

Erosion: moist red lesion due to loss of the superficial epithelium

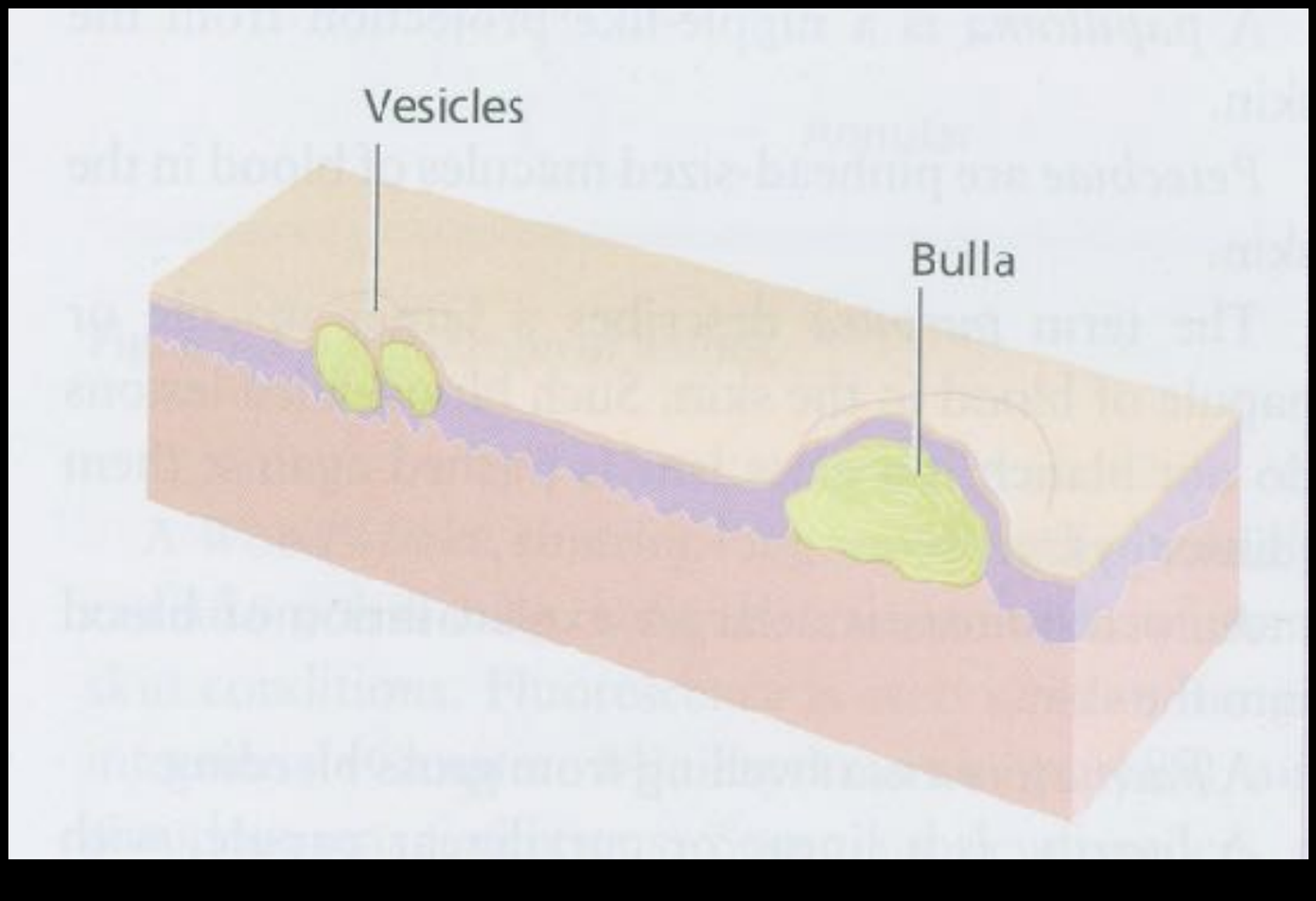
Ulcer: circumscribed depressed lesion over which the epithelium is lost



Nodule: lesion deep in submucosa, over-which the epithelium can be easily moved

Exophytic: growing upwards

Endophytic: growing downwards



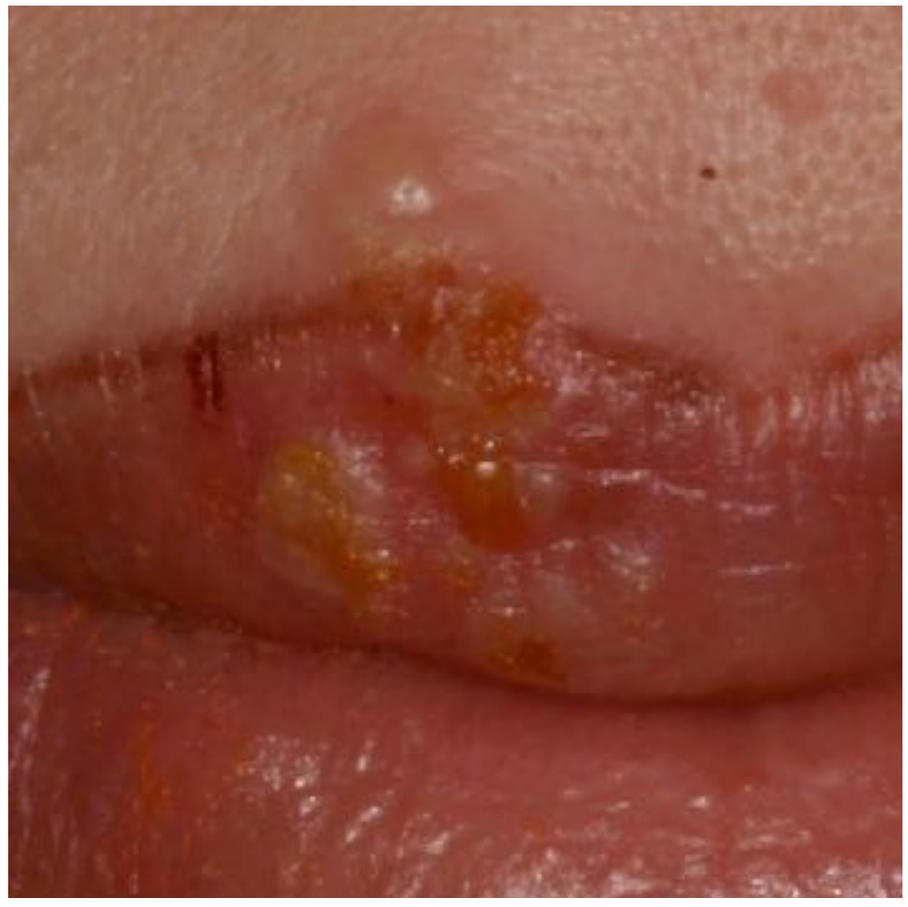
Vesicle: elevated blister containing clear fluid that is under 1 cm in diameter

Bullous: elevated blister containing clear fluid that is greater than 1 cm in diameter

Pustule: elevated lesion containing purulent material

Source: Clinical Dermatology. By Hunter el al 3rd ed. 2002

Clinical appearance of a ***Vesicle***



Clinical appearance of a ***Bullous***

A

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:
Fitzpatrick's Dermatology in General Medicine, 7th Edition: http://www.accessmedicine.com

History elements…

- Onset of the lesion
- Duration
- Progression
- Single or multiple
- Acute or chronic
- Pain
- Other systems involved; skin, eye, genitalia
- Family history
- Drug history
- Social history

Vesciulo-bullous Diseases

- Viral infection
  - HSV
  - VZV
  - HFM
  - Herpangina
  - Measles
- Immune-mediated
  - Pemphigus
  - Pemphigoid
  - DH
  - Linear IgA Disease
- Hereditary
  - Epidermolysis Bullousa

Viral infections

- Human Herpes viruses
- Coxsackie viruses
- Paramyxoviruses

Human Herpes Viruses HHV

- DNA viruses
- 80 types of Herpes viruses
- 8 types infect humans, six of those infect the head and neck area;

  HSV1, HSV2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8

Herpes virus	Target	Diseases
HSV-1	Mucosal epithelium	Herpetic gingivostomatitis
HSV-2	Mucosal epithelium	Genital herpes
VZV	Mucosal epithelium	Chickenpox and Shingles
EBV	B-cells and epithelium	Infectious mononucleosis, Burkett's lymphoma, OHL, NPCa
CMV	Monocytes and epithelium	Lymphadenopathy
HHV-6	T-lymphocytes	Roseolo infantum
HHV-7	T-lymphocytes	???
HHV-8	B-lymphocytes	Kaposi Sarcoma, lymphoma

Herpes Simplex Virus HSV 1

- Common viral infections
- Primary infection (systemic), and secondary infection (localized)
- Typical route of infection is physical contact
- Incubation period (IP) is 1-2 weeks

Herpes Simplex Virus HSV 1

- Primary infection is self-limited in the vast majority of population. Mainly seen in children.
- Virus then migrates to the trigeminal ganglion where it remains latent.
- Reactivation follows trauma, UV light, cold, stress, immune-suppression, and is usually localized.

Herpes Simplex Virus HSV 1

- Primary infection is characheterized by the eruption of small vesicles on any oral mucosal surface, including the gingivae (gingivostomatitis).
- It is wide spread and associated with clinical signs and symptoms (fever, headache, arthralgia, cervical lymphadenopathy, malaise…etc).
- Symptoms lasts for 7-10 days.

Herpes Simplex Virus HSV 1

- Secondary (recurrent) HSV
- Also called *Herpes Labialis* (usually affect the vermillion zone).
- Occurs when the immune system is altered unfavorably.
- Occurs in 40% of sero-positive persons.
- Prodromal symptoms: pain, itching, burning, tingling… etc at site of recurrence, then after few hours --> vesicles appear.
- Vesicles rupture and coalesce leaving an irregular ulcer, which heals in 1-2 weeks.

Intra-oral Herpes Simplex

Herpetic whitlow

- Direct contact to the skin
- Used to be seen in dental practitioners, prior to the use of examination gloves
- Causes severe pain, swelling and vesicular eruptions in the affected finger

Herpetic infection in the immuno-compromised

- More severe, destructive vesicles and ulcers which are not restricted to the oral cavity
- Due to compromised immune response; HIV, chemotherapy, immune suppressive medications…etc

Herpes Simplex Virus HSV 2

- Predilection to genital mucosa, but might also infect oral mucosa following oro-genital contact
- Latency occurs when HSV 2 travels to the lambo-sacral ganglion
- Clinically and histologically indistinguishable

Histopathology

- Intra-epithelial blisters, containing dead epithelial cells, inflammatory cells and exudate.
- Inclusion bodies can be seen in keratinocytes.

Erythema due to inflammation

Multiple errosions and coalesence

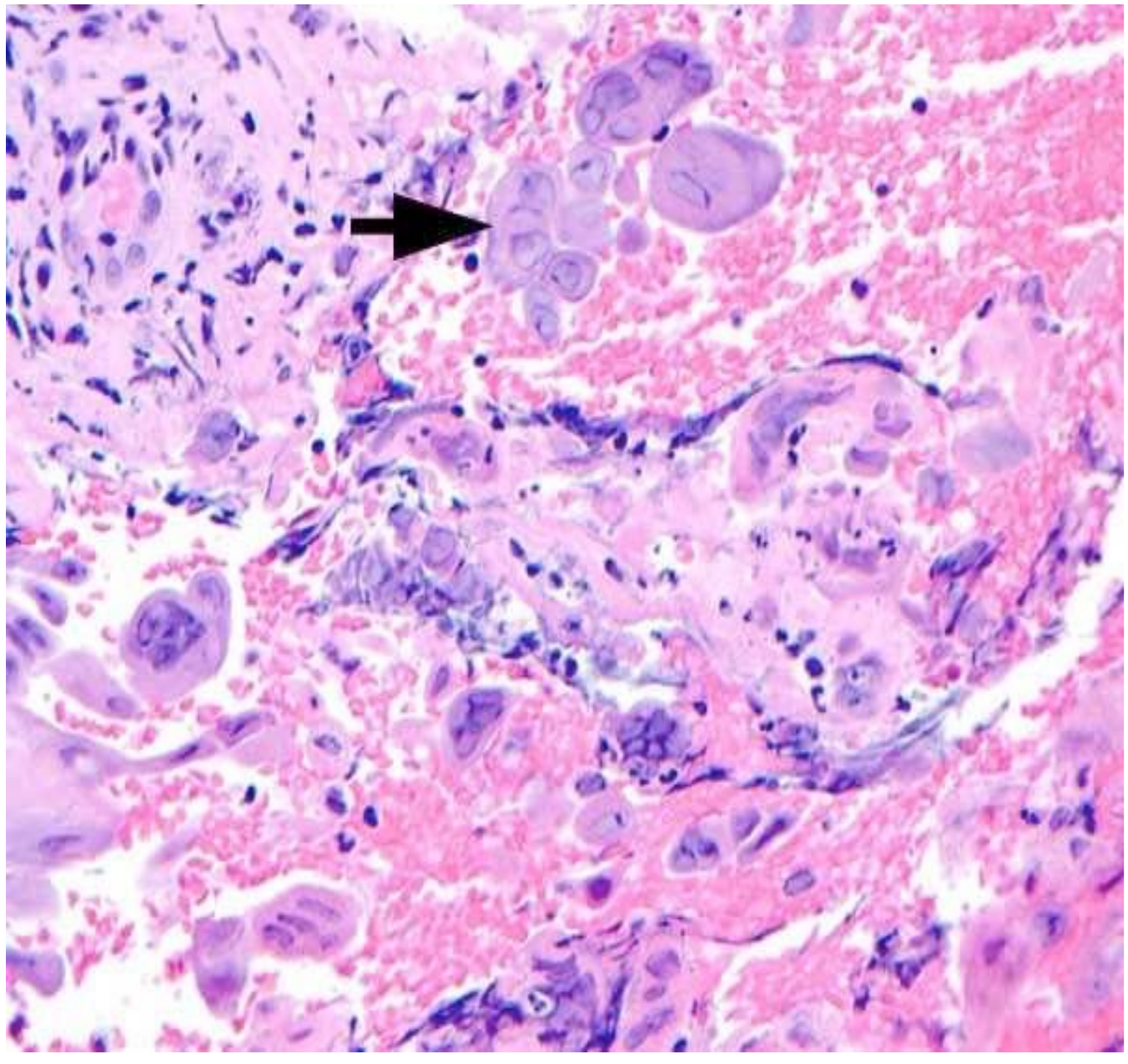


Image source: pathpedia.com

QUESTION: HOW DO WE COMPARE BETWEEN ZOSTER VIRUS and HERPES

ANS:

Zoster	Herpes
- More severe	- Less severe
- Large area	- Small area
- More painful	- Less painful
- Past infection compli.	- Infect, erupt, cause vesicles then ulcers then go away
- Perm damage (scar)	- No permanent damage
- Airborne	- Direct contact (transmission)
- Less Frequent	- More Frequent
- Seen in elderly & Immune suppressed	

Case: A lesion that doesn't cross midline (right side only)

- Affect upper third of the face
- Eye is red & swollen (upper eyelid)

=> Affects the ophthalmic branch of the trigeminal nerve.

NB] Usually patients with 2ndary infection are immunocomprimised so always if any patient comes to you with shingle then he/she is immunocompromised or are taking medications that suppress the immune system or have diseases that reduce immunity.

Treatment

Acyclovir can be topical
or systemic (for immunocompromised pts)

- Supportive therapy for primary infection.
- Acyclovir for treating severe systemic infections, or to reduce the duration of the recurrent infections.
- Acyclovir activated by thymidine kinase (produced by herpes viruses), therefore it inhibits DNA polymerase in infected cells and not in healthy cells.
- Topical: 5% Acyclovir 5 times/day.
- Systemic: 200-400 mg 5 times per day (immune compromised).
- Should be used as early as possible.

Question: How can acyclovir only inhibit DNA in the affected cell?
Ans: by the thymidine kinase which is found only in the affected cell.

Reference: Bouquot JE, Horn N, Wan S-F. Herpes zoster. Texas Dent J 2007; 124:132, 136-138.

Varicella-Zoster virus VZV

affect ophthalmic branch of trigeminal nerve.

- Primary infection: varicella or chickenpox
- Secondary (recurrent) infection: zoster or shingles
- Typical route of transmission is airborne
- Highly contagious
- IP is 2 weeks

Image source: reference.medscape.com

chickenpox result in rash and vesicles throughout the body and on the face

Image source: wikipedia.org

Varicella (chickenpox) infection

- Childhood disease
- Associated with systemic signs and symptoms (fever, malaise, headache, rash…etc)
- rash --> vesicles --> pustules --> ulcers

it ruptures causing v

red spot

2nd infection will be soft and tender

All stages seen together

- Self limiting, last for few weeks
- Pruritic urgue to scratch

in some pts after recovery the area of skin can result in pigmentation called post herpetic pigmentation or neuralgia.

Zoster (shingles) infection

- Elderly disease
- Compromised?
- Affects the trunk and H&N (latency in sensory ganglion or trigeminal nerve)
- Prodromal symptoms --> pain, tingling, parasthesia --> maculopapular rash --> vesicular --> pustular --> ulcers

2ndary infection ->

- Consequences: scar, post-herpetic neuralgia, infection, hyperpigmentation, paralysis

nerves are damaged

Zoster (shingles) infection

upon 2ndary infection

vesicles and ulceration are inside the ear or around the ear. complication is deafness this is due to nerve damage

- If latency at CN VII and VIII --> Ramsay Hunt syndrome

Mage source: emedicine.medscape.com

Mage source: otoscopy.hawkelibrary.com

Complications: paralysis in facial nerve & develop weakness in 1 side of face
severe pain
deafness

Treatment

- Varicella: self limiting
- Zoster: Acyclovir (800 mg five times / day)
- Systemic Corticosteroids are used, with or without antiviral drugs, for the treatment of Ramsy Hunt syndrome

The only time where we accept the use of corticosteroids to suppress of the overactivity of the immune system is here

MUST TAKE CARE NOT TO SUPPRESS THE IMMUNIT BECAUSE THIS WILL HELP THE VIRUS REPLICATE MORE

Hand Foot and Mouth disease

Similar ulcers on hand and feet as the ones in the mouth (characteristic feature)

- Caused by Coxsackie virus (A16 mainly)
- Highly contagious, by airborne and oro-fecal routes
- Affects children
- Prodromal symptoms, followed by:
  - Oral lesions: oral vesicles (anywhere) --> ulcers
  - Skin lesions: maculopapular rash (hands and feet) --> vesicles --> ulcers

Treatment

- Symptomatic
- Bland mouthwash

if in pain give pain medications

Herpangina

usually posterior area of mouth

- Caused by Coxsackie virus
- Transmitted by saliva and possibly oro-fecal routes
- Affects children
- Endemic and seasonal (summer and early autumn)
- Vesicles (soft palate faucial pillers, tonsiles) --> ulcers + pharyngitis + sore throat, dysphagia
- Mild and short infection
- Treatment is symptomatic

Measles

tiny vesicles on the buccal mucosa with an erythematous background (herpangina)

- Caused by Measles virus (Paramyxovirus family)
- Airborne infection
- Affects children
- Seasonal (winter and spring)
- Prodromal symptoms: cough, fever, malaise, conjuctivitis

temporary because after their appearance there 2-3 days before rash appears on the body

- IP = 7-10 days, after 1-2 days --> Koplik's spots, then after 1-2 days --> maculopapular rash starting head to trunk to extremities
- Treatment is symptomatic

vesicles infected by viruses

Vesciulo-bullous Diseases

Viral infection

- ~~HSV~~
- ~~VZV~~
- ~~HFM~~
- ~~Herpangina~~
- ~~Measles~~

prodormal symp.

Immune-mediated

- Pemphigus
- Pemphigoid
- DH
- Linear IgA Disease

absence of prodormal symp and middlge ages

Hereditary

- Epidermolysis Bullousa

ask whether it's from birth
ask about family history

Pemphigus

problem with this disease is it's difficult to see the vesicle itself

- Auto-immune disease
- Mucocutaneous skin and mucosa
- Four subtypes;
  - p. vulgaris most severe and most common in oral cavity
  - p. vegetans
  - p. foliaceus
  - p. erythematosus
- Oral mucosa --> p. vulgaris, to lesser extent p. vegetans
- A rare subtypes: Para-neoplastic Pemphigus (PNP)

where the autoimmune disease is initated by an underlying malignancy

Pemphigus

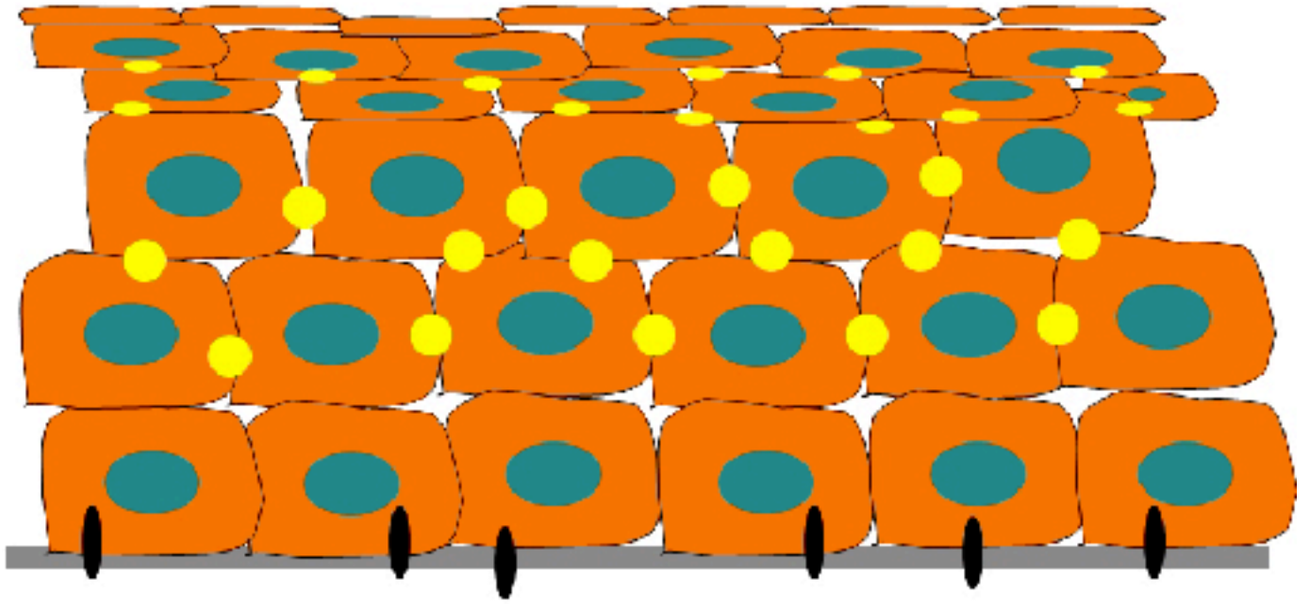
IgG attacks the desmosomes & protein to bind the .... and this will separate the struction of epithelium (stratum spinosum) from CT

Pathogenesis;

- Antibodies, mainly IgG, become reactive to desmoglein 3 (an inter-cellular adhesion glycoprotein belonging to cadherin family) at the stratum spinosum layer.

central part of epi. which is the strongest part is damaged!!!

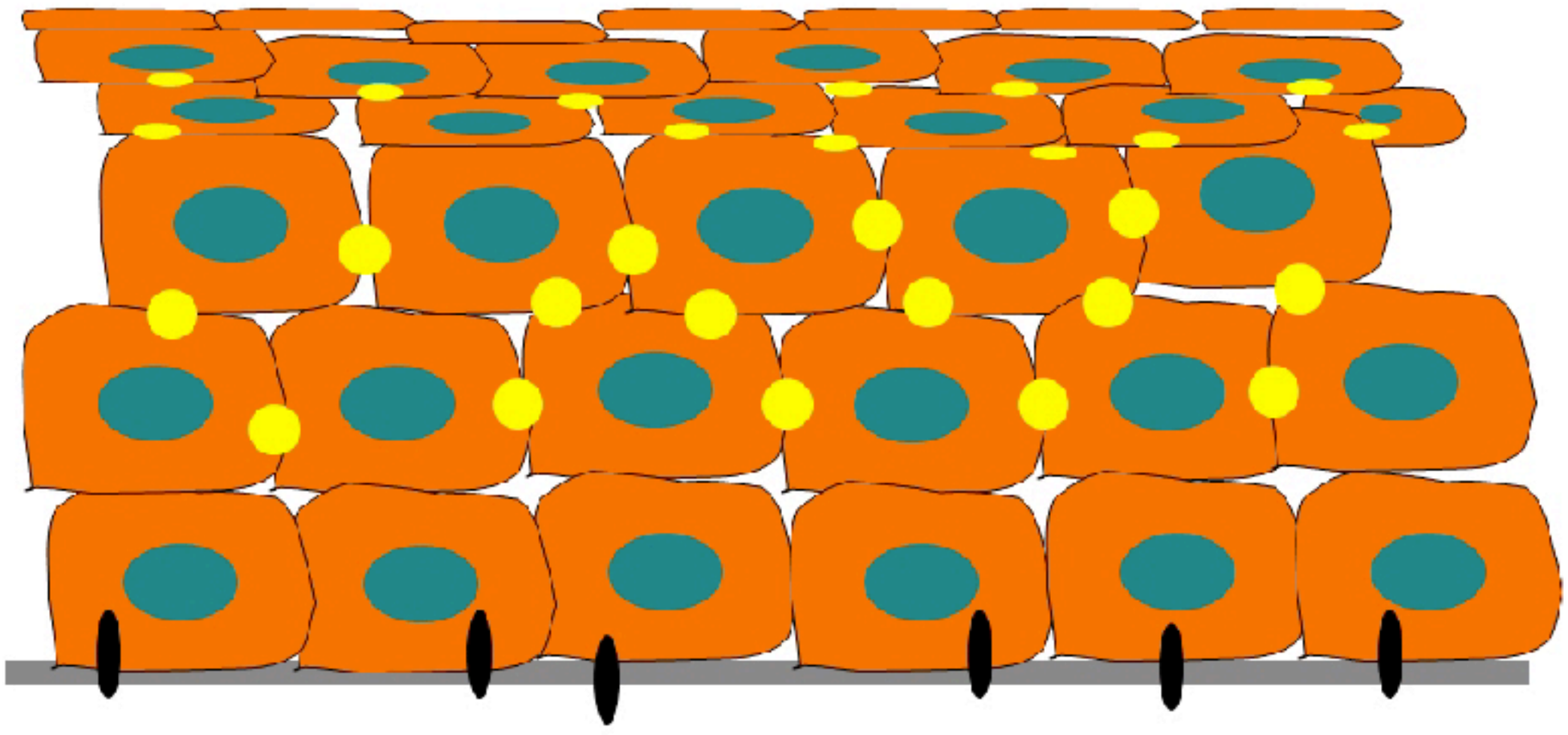
- This reaction will result in non-functional desmosome
- Loss of cell-cell attachment --> acantholysis
- Blister formation



autoimmune disease attacking the epithelia and causing it to separate from the CT

NB] Stratum basale cells are not effected and will intact. only what's above them is attacked.

Question: how do you make sure it's caused by auto-immune disease not an artifact?
Ans: auto-immune diseases antibodies are present and this is done by direct immunofloroscence.



how pemphigus affects the skin?
-> vessicles on skin
-> Area of erosion

Source: McPhee SJ, Papadakis MA: *Current Medical Diagnosis and Treatment 2009,* 48th Edition: http://www.accessmedicine.com

Pemphigus

erosions are seen & not ulcers because it only affects the area above the basement membrane where ucler is comp. loss of epithelium.

Pathogenesis

- Possible genetic predisposition;
  - Higher incidence among Ashkenazi Jews, Mediterraneans and Asians
  - Persons with certain MHC types (HLA-DR, HLA-A10, HLA-DQB, HLA-DRB1)
  - Association with other autoimmune diseases;
    (Myasthenia Gravis MG, Systemic Lupus Erythematosus SLE, Rheumatoid Arthritis RA, Sjögren Syndrome SS…etc)
  - A hereditary variant (Hailey-Hailey disease)

Pemphigus

Clinical presentation

- Patients are 40-60 years, equal gender
- Bullae that rupture very quickly (within minutes of forming)
- PV appears first in oral mucosa in 60% of patients before appearing in skin

First to show, last to go

The inital presentation before skin is the mouth

If given a corticosteroid and an immpunosupressant {corticosteroids, cyclosporin}
Which has greater risk?

Answer: cyclosporin because it only supresses the immune system which is one system, however corticosteroids affect the whole body

Then why do we start with corticosteroids?

- Widespread erosions affecting all oral and oro-pharyngeal mucosae
- Positive Nikolsky's sign
- Very painful and risk of infection and electrolyte imbalance if untreated.

Induce the blister by oneself by stretching and use mirror/ finger & rub the cheek because the epithelium is already separated & by rubbing, the space will be filled without fluid or blood.

.

.

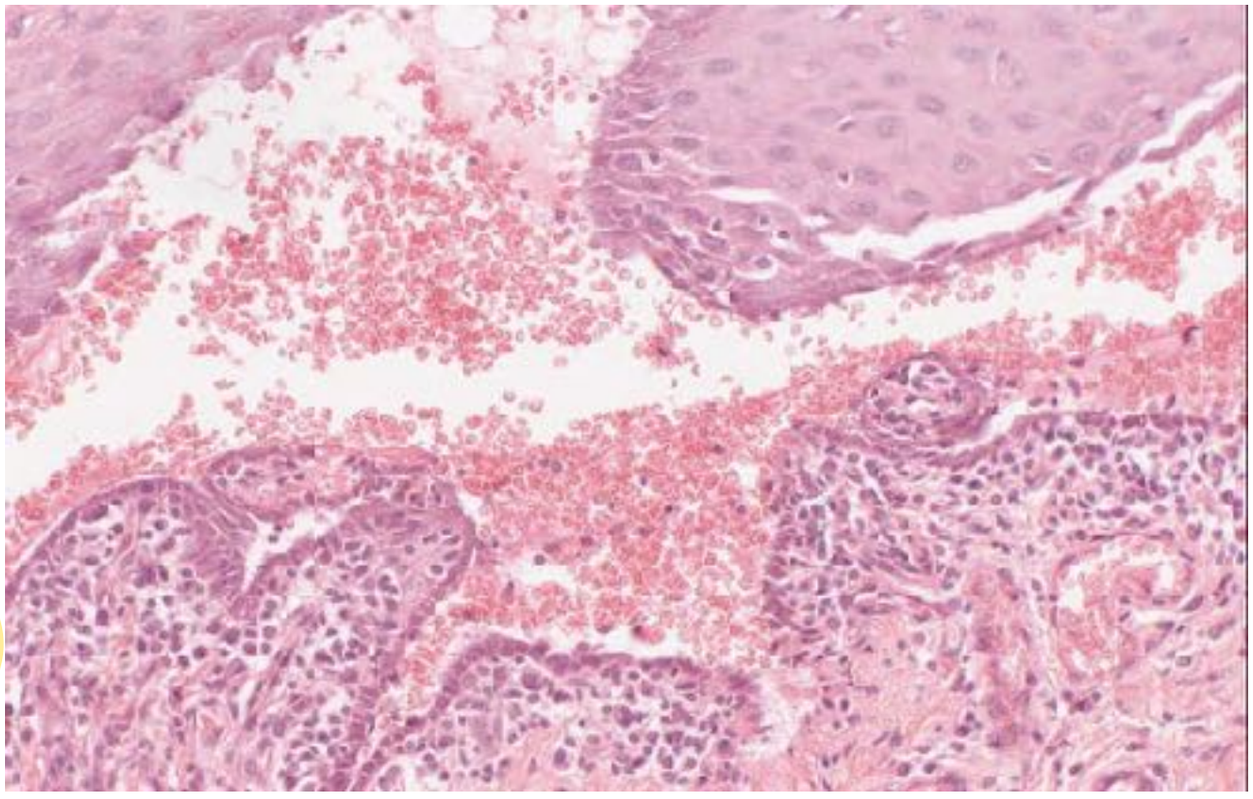
Not very good because we induce the disease itself.

Problems are with electrolyte imbalance and loss of fluid` 2ndary bacterial infection.

Pemphigus

Histopath.

- Bullous, with acantholytic cells (Tzank cells)
- Intact basal cell layer
- Positive DIF (IgG, and to less extent IgA and C3 surrounding the cell membrane at the stratum spinosum)
- Occasionally positive IIF (circulating auto-antibodies in serum)



Pemphigus

surface epithelia will shed

Treatment;

- Topical cortico-steroids
- Systemic cortico-steriods
- Immune-suppressants
- Plasmapheresis

used as last method of treatment. We take the pts blood and then clear it from all the antibodies then return it.

Complications of systemic cortico-steroids

very strong in controlling the disease

we can't keep treating patients with corticosteroids so we start with them to control disease then decrease them and increase immunosuppressants

- Hyperglycemia
- Hypertension
- Hyperlipidemia
- Muscle wasting
- Redistribution of fat; moon face, buffalo hump

Affect almost every single part of the body
But very effective

- Peptic ulcer
- Osteoporosis
- Glaucoma and cataract
- Psychological changes
- Adrenal atrophy
- Candidosis
- Mucosal atrophy

Pemphigoid

the feeling of the vesicle is rough/tough and remains for a little longer before it ruptures

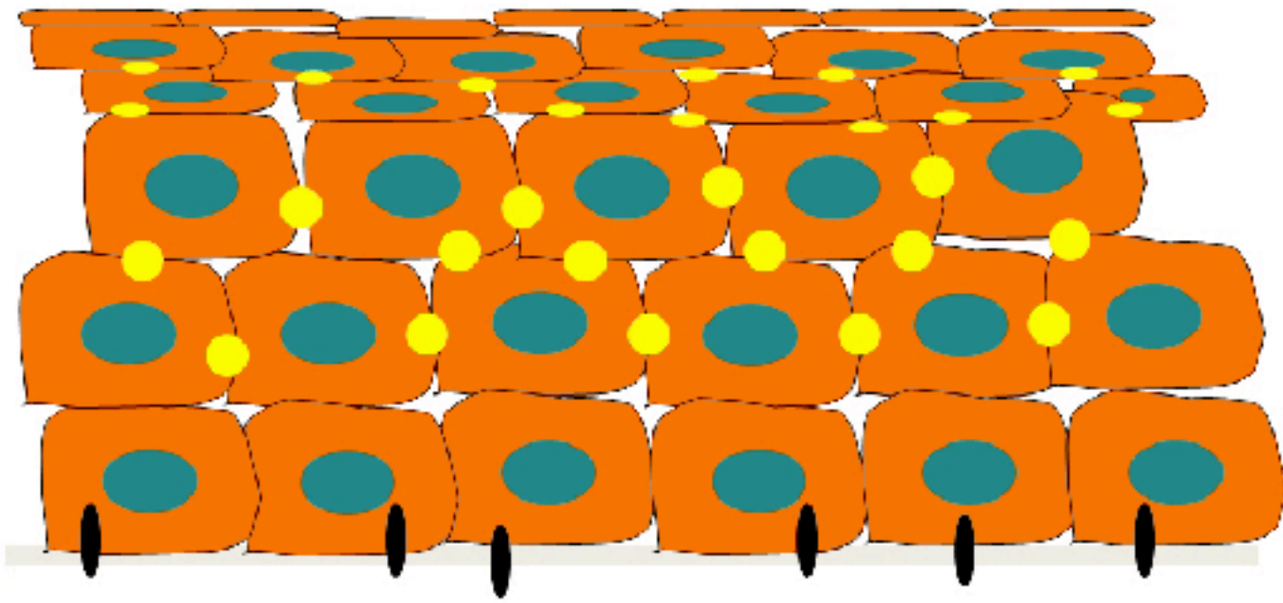
- Autoimmune
- Chronic mucocutaneous disorder
- Two subtypes; mucous membrane pemphigoid, (MMP) and bullous pemphigoid (BP)
  - MMP mainly affects oral and ocular mucosae. Also called; cicatricial pemphigoid
  - BP mainly affects the skin

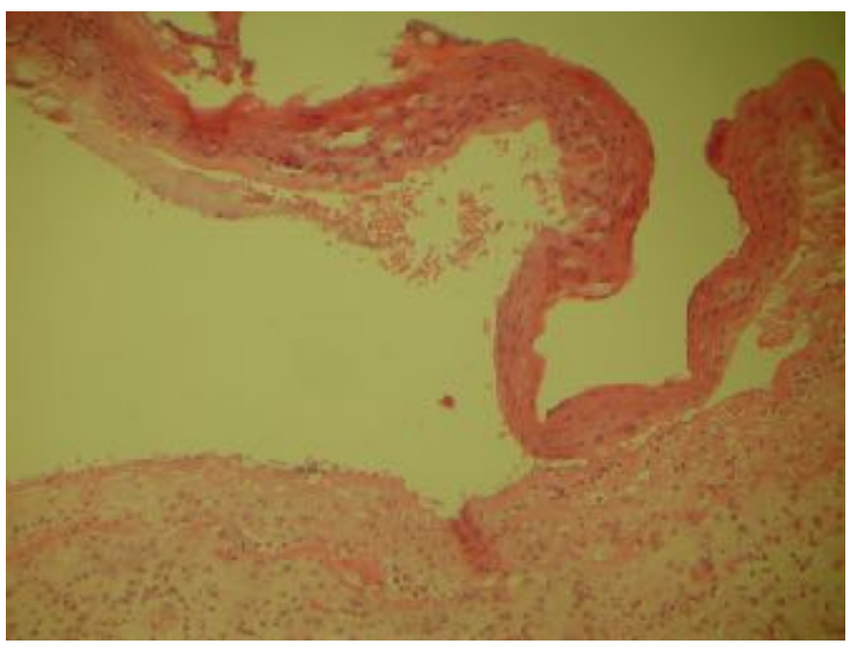
Q] Which is less severe? Pemphigus or Pemphigoid
A] Pemphigoid because it's localized only 1-2 lesions throughout the mouth.

MMP

Complete separation of the entire epithelia and will cause an ulcer.
it affects oral cavity
it's releated to the eyes

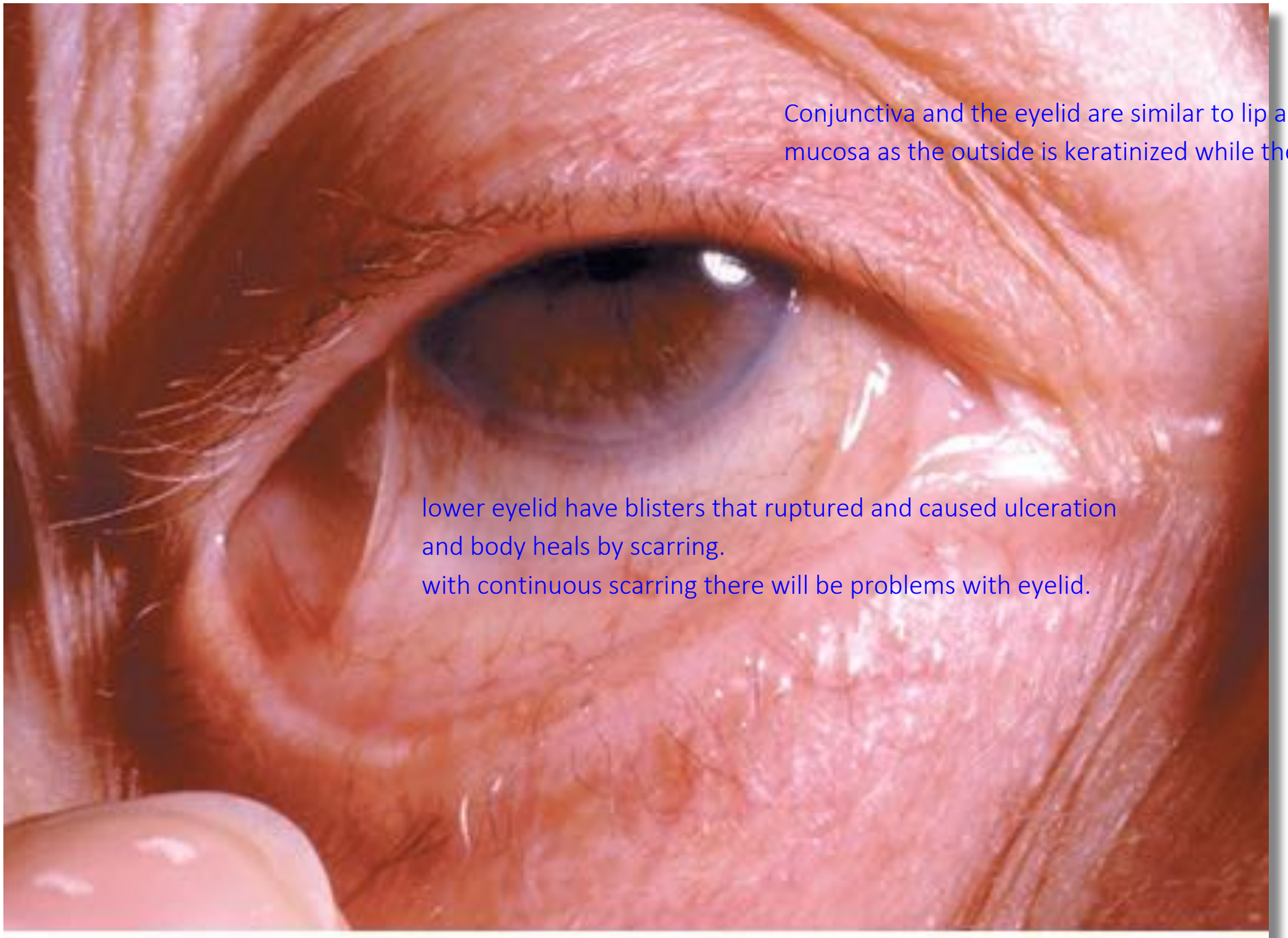
- Immune-globulins, mainly IgG, react to hemidesmosomes at the basement membrane, mainly Laminin 5 and BP 180 proteins.
- This reaction results in loss of adhesion between the basal cell layer and the basement membrane, and separation of the epithelium from the underlying connective tissue.





MMP

- Clinically, MMP affects the adults and elderly with female predilection
- Orally, short-lived blisters which produce irregular superficial ulcers
- Sometimes the gingiva is the only oral tissue affected, resulting in desquamative gingivitis
- Positive Nikolsky's sign



Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

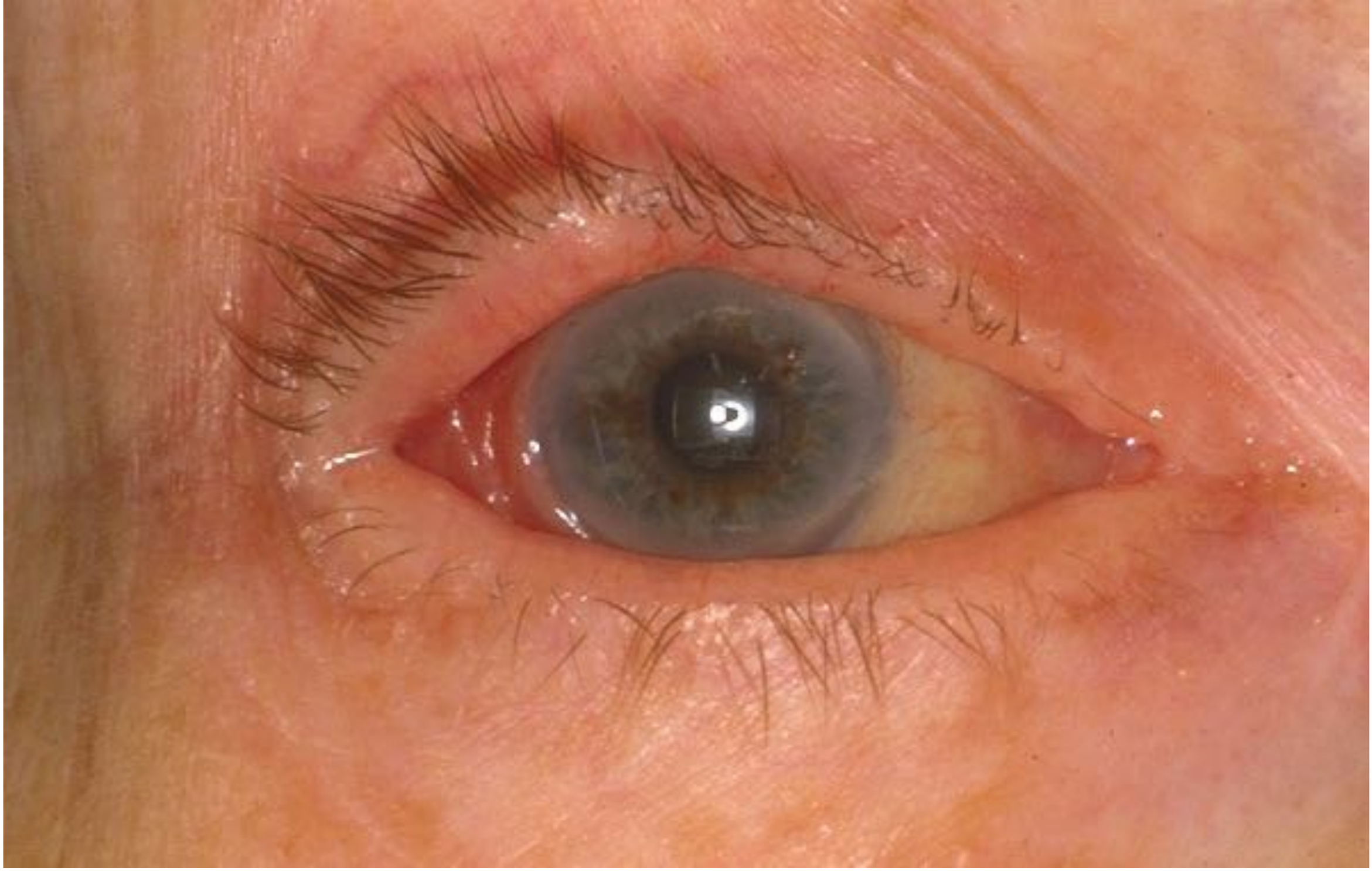
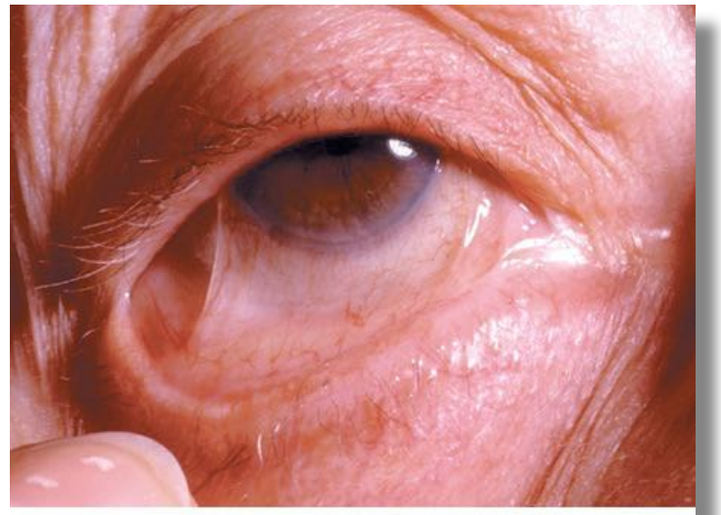


Image source: medscape

When pemphigoid is diagnosed must check with ophtalmology



- Healing might cause a scar (cicatrix)
- Scarring of the canthus of the eye (symblepharon) is a serious outcome and can lead to blindness
- Other tissues; larynx, genitalia and rarely skin

BP

- Mainly affects the skin, uncommonly the oral mucosa
- Patients are 70-80 years
- Tense vesicles and bullea
- Also resulting in separation of the epithelium from the underlying connective tissue
- The antigen target is BP 230 and BP 180
- The reaction is at a higher level of lamina lucida

A

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:
Fitzpatrick's Dermatology in General Medicine, 7th Edition: http://www.accessmedicine.com

MMP and BP

- Histopathologically indistinguishable
- Subepithelial clefting, no acantholysis
- DIF shows homogeneous linear pattern at the basement membrane zone
- IIF is usually negative

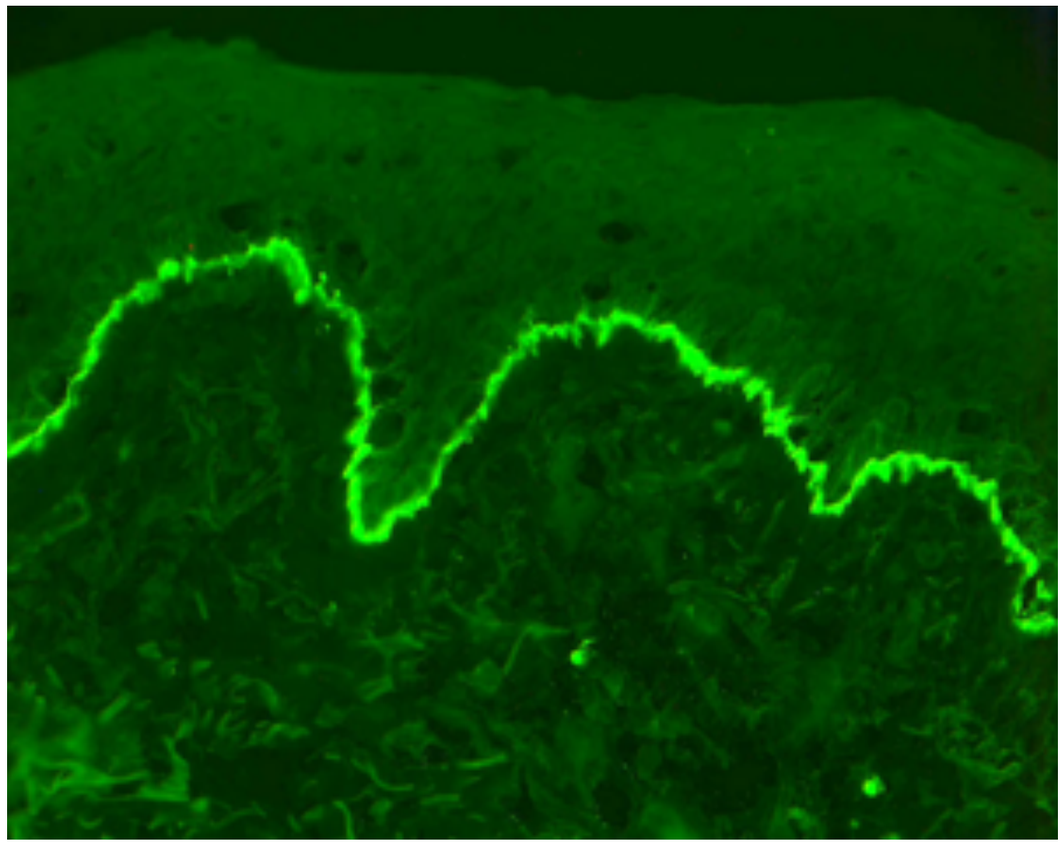


Image source: medicine.utah.edu

Treatment

- Ophthalmology consult
- Maintain high standard oral hygiene
- Topical corticosteroids
- Systemic corticosteroids
- Immue-suppressants

Differential diagnosis of desquamative Gingivitis DG

must consider the possibility of mucous membrane pemphigoid.

- Mucous Membrane Pemphigoid MMP
- Pemphigus Vulgaris PV
- Oral Lichen Planus OLP
- Lupus Erythematosus LE
- Contact allergy

Linear IgA Disease LAD

similar to MMP but antibody is IgA (not IgG)

- Autoimmune disease
- Affects the skin and the oral and ocular mucosae
- IgA reacts to the antigen target at the basement membrane 120 Kd protein, resulting in clefting and separation of the epithelium from the connective tissue

Linear IgA Disease LAD

- Clinically, there are skin and mucosal ulcerations preceded by vesicles and/or bullae
- Diagnosis is based on biopsy and DIF (showing a linear pattern of IgA antibodies at the basement membrane level)
- The cleft is filled with neutrophils and eosinophiles

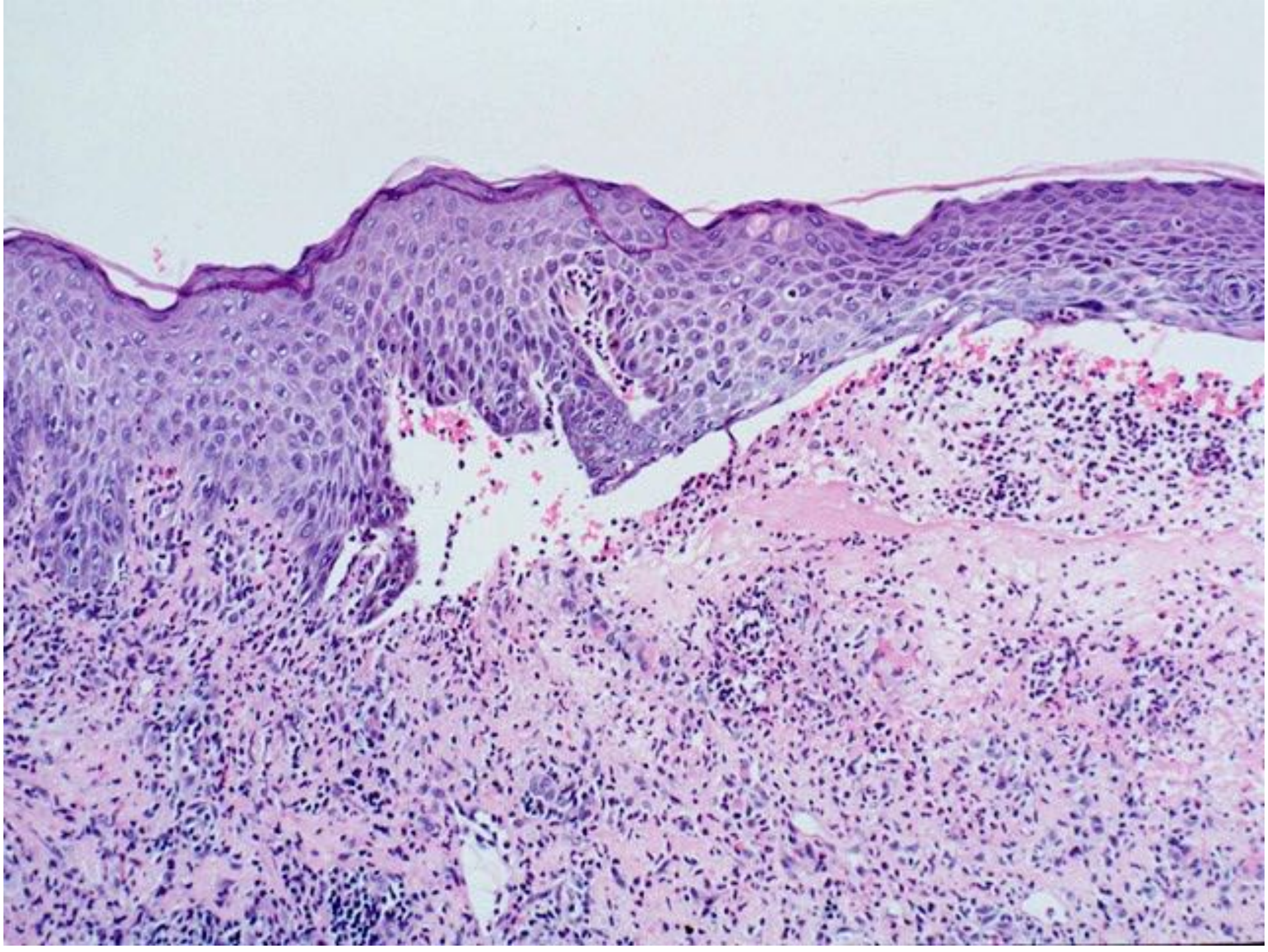


Image source: medscape

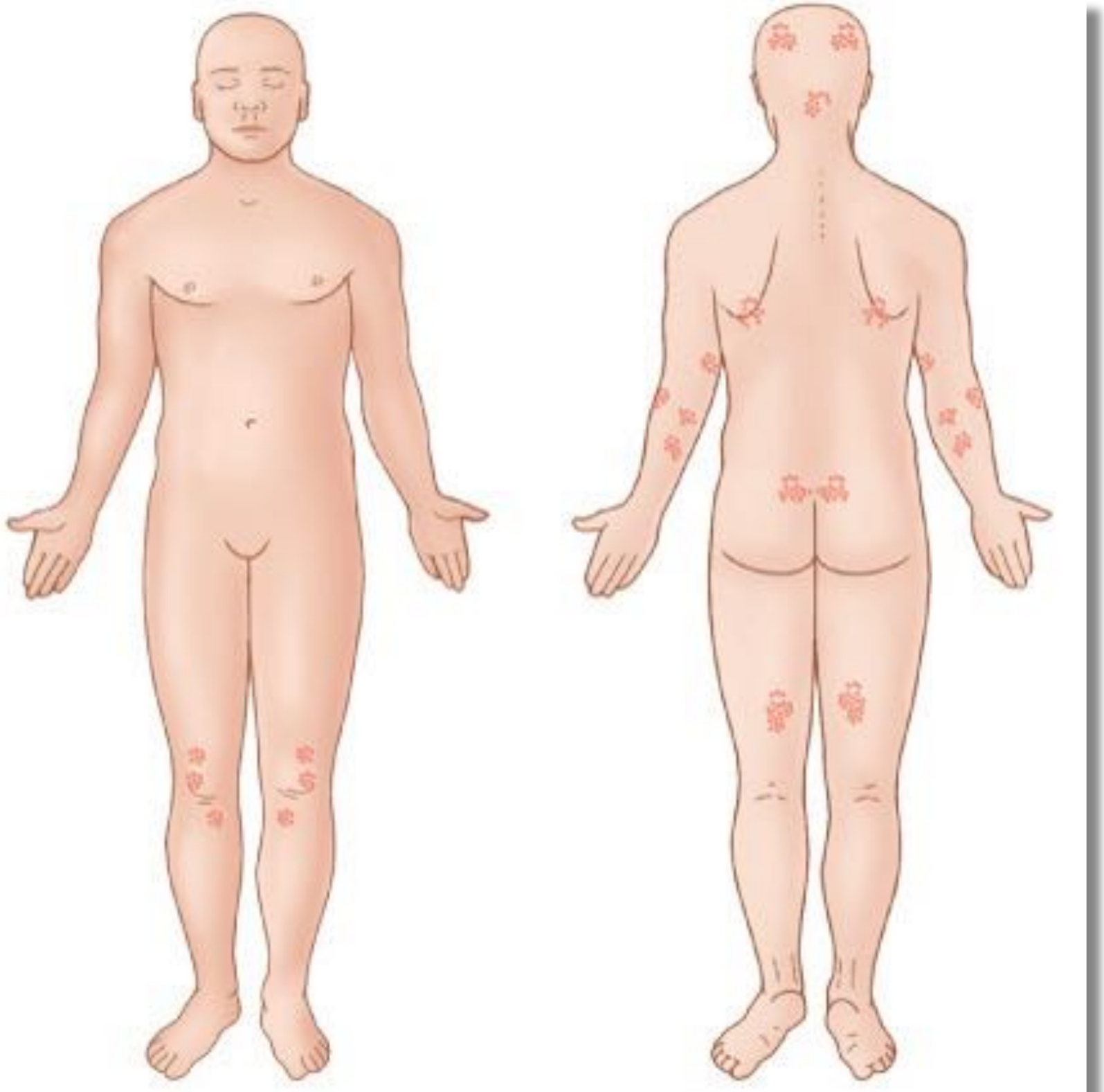
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Dermatitis Herpetiformis DH

with repeating

- Autoimmune disease or an immune-dysfunction
- Affects middle aged, with a male predilection
- Affects the skin and very rarely oral mucosa
- Clinically, erythematous vesicles on the shoulders, elbows, buttocks that are extremely pruritic, and that wax and wane
- Oral lesions; vesicles rupturing into ulcers
- Association with gluten-sensitive enteropathy
- Granular deposits of IgA antibodies at the basement membrane

with repeated rupture and scarring this will cause a problem in the erruption of teeth because the gingiva will be full of fibrotic tissue



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Vesciulo-bullous Diseases

- Viral infection
  - HSV
  - VZV
  - HFM
  - Herpangina
  - Measles
- Immune-mediated
  - Pemphigus
  - Pemphigoid
  - DH
  - Linear IgA Disease
- Hereditary
  - Epidermolysis Bullousa

Hereditary Diseases
Epidermolysis Bullosa

- Genetic defects of the basal keratinocytes, hemi-desmosomes, or the connective tissue filaments
- Three types: dystrophic, junctional, and simplex
- Can be autosomal dominant or autosomal recessive
- Onset at infancy or childhood
- Bullae develop over areas subject to trauma

Image source: medscape

Hereditary Diseases
Epidermolysis Bullosa

- Oral lesions are common in the recessive form, they cause bullae --> ulcers --> scar tissue
- Constricted oral orifice, hypoplastic teeth, malnutrition…etc. due to continuous scarring
- Treatment;
  - avoid trauma, supportive therapy
  - corticosteroids, chemotherapy, retinoids, Vt E --> limited benefit.

Image source: medscape

Vesciulo-bullous Diseases

- Viral infection
  - HSV
  - VZV
  - HFM
  - Herpangina
  - Measles
- Immune-mediated
  - Pemphigus
  - Pemphigoid
  - DH
  - Linear IgA Disease
- Hereditary
  - Epidermolysis Bullousa

Reading material;

Regezi, sciubba & Jordan.

Oral Pathology Clinical Pathologic Correlations, Chapter 1.