Pemphigus

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Definition

- Pemphigus is a group of autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intraepidermal blisters due to acantholysis (separation of the cells from each other) and immunopathologically by in vivo bound and circulating IgG directed against the cell surface of keratinocytes.

Overview

- Pemphigus (from the Greek *pemphix, meaning bubble or* blister) is a rare group of autoimmune, intraepidermal blistering diseases involving the skin and mucous membranes.
- The group includes 2 polar forms pemphigus vulgaris and pemphigus foliaceus.
- Both were usually fatal before glucocorticoid therapy was used for their treatment. The difference between the two disorders is the level of the epidermis at which acantholysis (loss of cohesion of epithelium) occurs:
  - the suprabasilar level in pemphigus vulgaris, and
  - the subcorneal level in pemphigus foliaceus.
- Other members of the pemphigus group are paraneoplastic pemphigus, which generally occurs in patients with lymphoma, and drug-induced pemphigus, which usually develops after taking penicillamine.

Epidemiology and Etiology

- Age of onset: 40 to 60 years
- Sex: equal incidence in males and females
- Etiology: autoimmune disorder

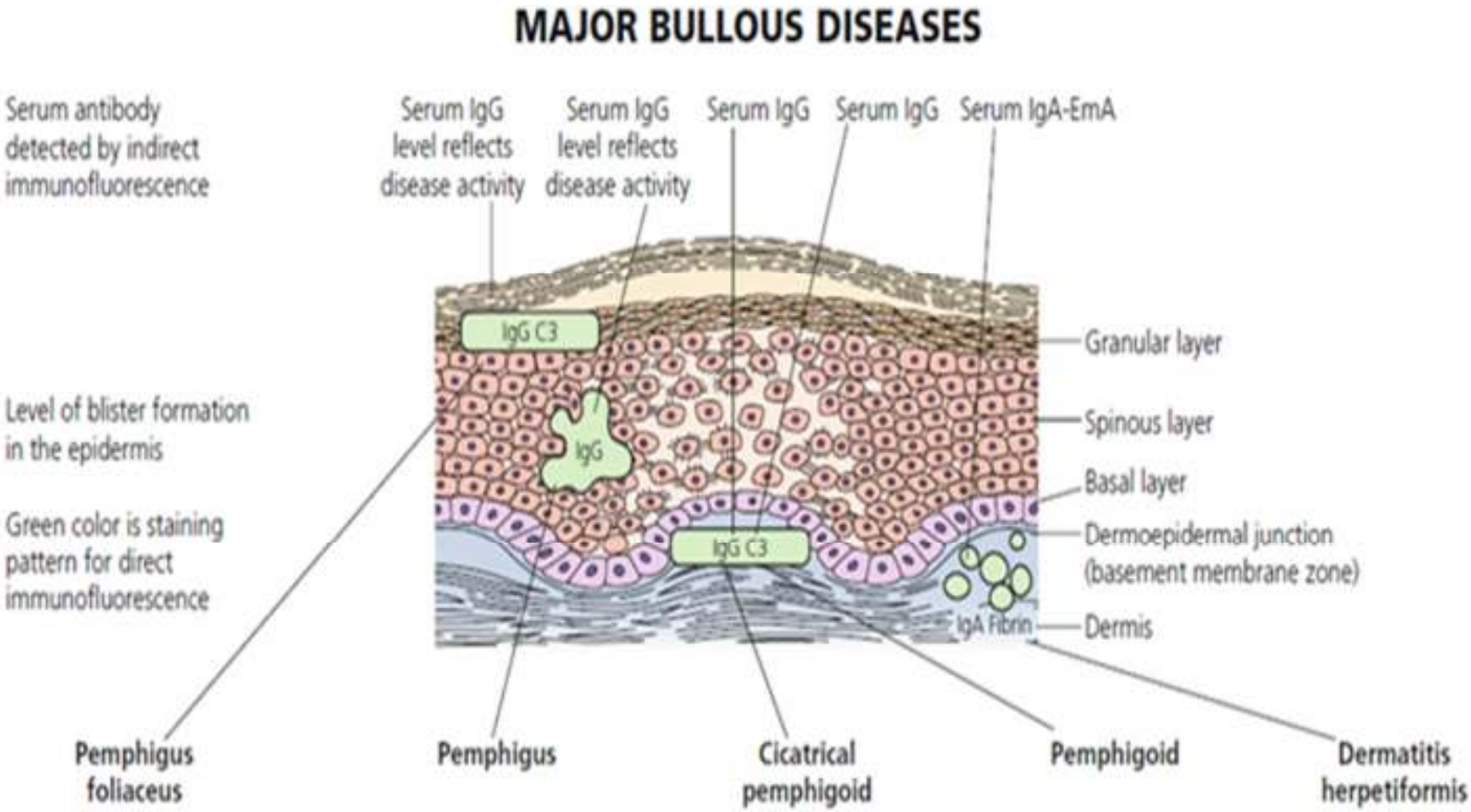
Patophysiology

- Pemphigus is the result of the interaction between genetically predisposed individuals and possibly some exogenous factor.
- The presence of foci of pemphigus foliaceus (fogo selvagem) in rural South America suggests that the disorder can be triggered in susceptible persons by an environmental agent (probably an unidentified infectious agent), whose antigens mimic those of desmoglein 1, and that clinical disease evolves in the persons who have the most vigorous immune response to desmoglein 1.
- Both idiopathic pemphigus and induced pemphigus have the same human leukocyte antigen (HLA) pattern.
- Among Ashkenazi Jews with PV, the serologically defined HLA-DR4 haplotype is predominant, whereas in other ethnic groups with PV, the DQ1 allele is more common.

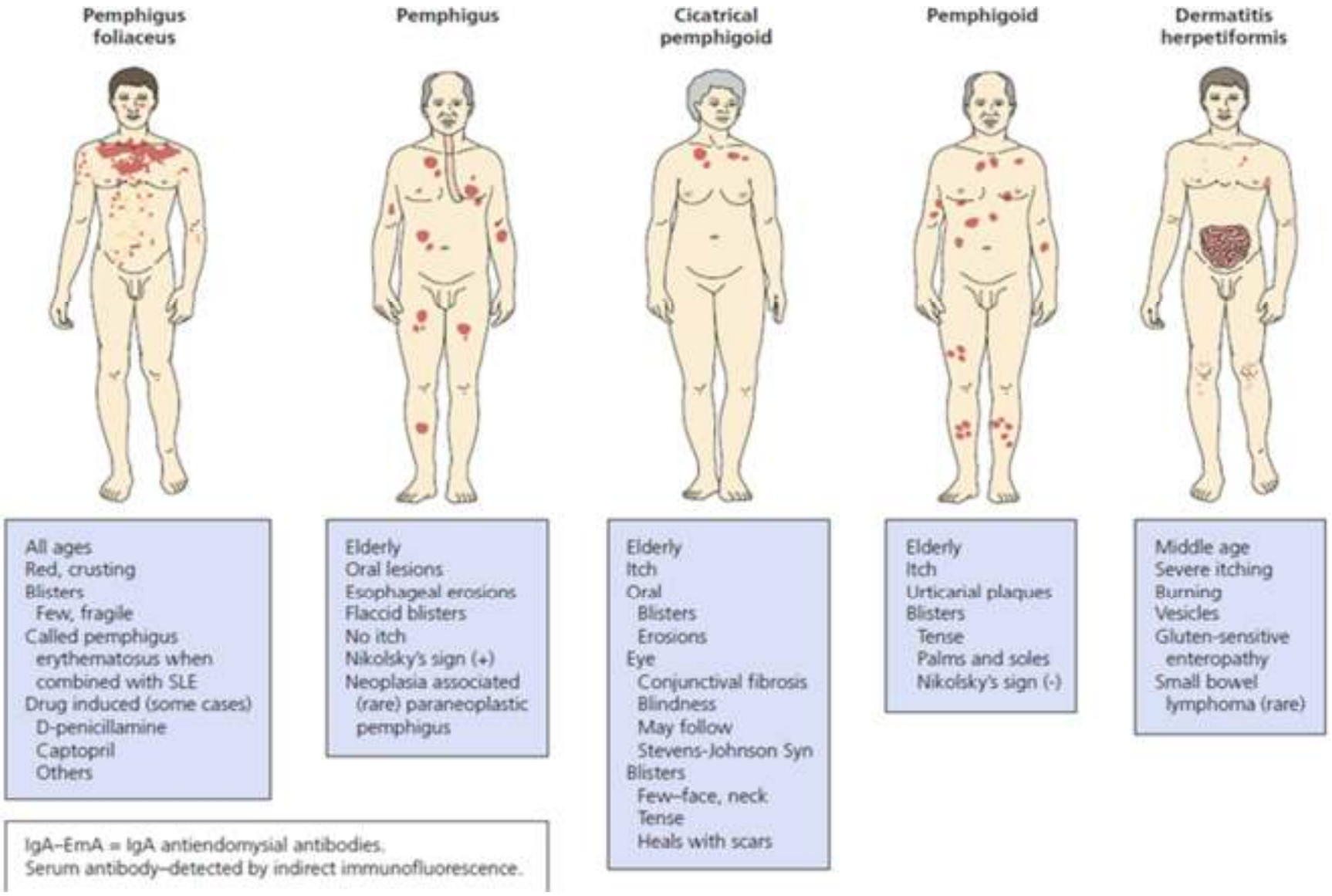
Pathogenesis

- A loss of normal cell-to-cell adhesion in the epidermis occurs as a result of circulating antibodies of the IgG class;
- These antibodies bind to cell surface glycoproteins of the epidermis and induce acantholysis, probably by the activation of serine proteases;
- The superficial subtypes of pemphigus are associated with autoantibodies to desmoglein 1, a 160 kD transmembrane desmosomal component;
- The deep subtypes of pemphigus are associated with autoantibodies to desmoglein 3, a 130 kd transmembrane desmosomal component, and to desmoglein 1.

Pathogenesis of skin bullous diseases



Clinical correlations in skin bullous diseases

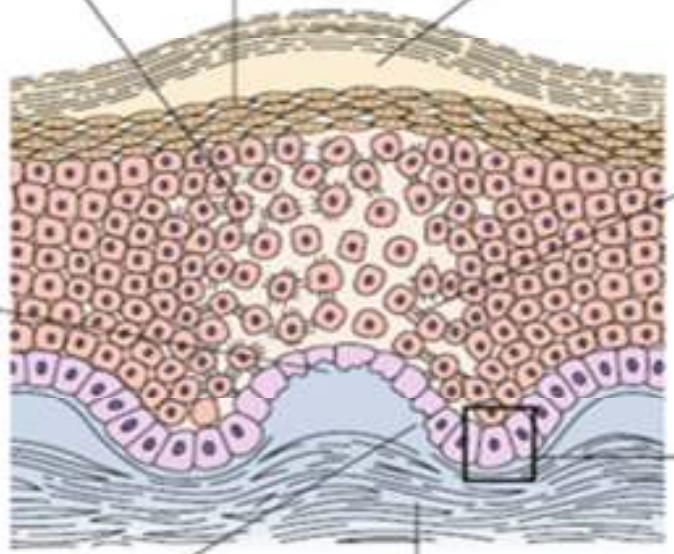


BULLOUS DISEASES IN THE EPIDERMIS AND DERMOEPIDERMAL JUNCTION

Spinous layer (upper and mid-epidermis)
Dermatophyte fungous infection
Dyshidrosis
Eczematous blister
Friction blister
Insect bites and scabies
Miliaria rubra
Viral blisters (herpes simplex, zoster)

Granular cell layer
Bullous ichthyosiform erythroderma
Pemphigus foliaceus
Pemphigus erythematosus

Subcorneal
Candida albicans infection
Impetigo
Miliaria crystallina
Staphylococcal scalded skin syndrome
Subcorneal pustular dermatosis



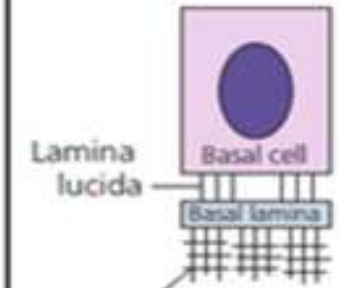
Basal cell area
Erythema multiforme (epidermal type)
Epidermolysis bullosa simplex
Fixed drug eruption
Kerosene necrosis
Lichen planus
Toxic epidermal necrolysis

Spinous layer (lower epidermis and suprabasal area)
Benign familial chronic pemphigus
Keratosis follicularis
Pemphigus vulgaris
Transient acantholytic dermatosis

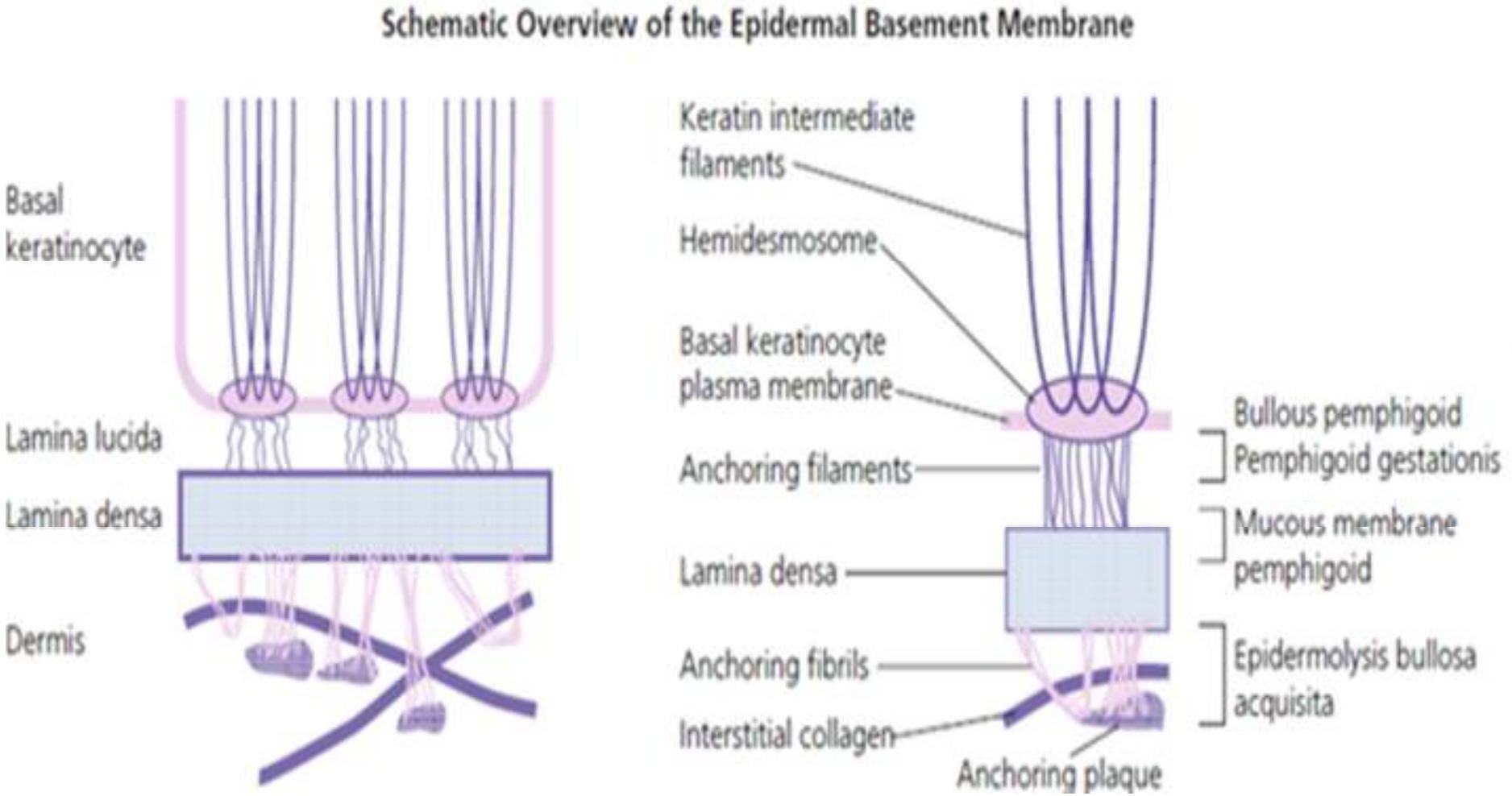
Lamina lucida
Bullous pemphigoid
Cicatrical pemphigoid
Dermatitis herpetiformis
Epidermolysis bullosa acquisita
Epidermolysis bullosa letalis
Herpes gestationis
Suction blister
Thermal lesions (burns, cold, e.g., liquid nitrogen)

Basal lamina and sublaminar connective tissue
Bullous dermatosis of hemodialysis
Bullous eruption of SLE
Epidermolysis bullosa dystrophica
Erythema multiforme (dermal type)
Ischemic bullae (drug overdoses)
Lichen sclerosus et atrophicus
Porphyria cutanea tarda

Ultrastructure of dermoepidermal junction



Basement membrane bullous skin diseases



Molecular classification of pemphigus

Pemphigus type	Target desmosomal protein
Pemphigus vulgaris	Desmoglein 3 (and desmoglein 1)
Pemphigus foliaceus	Desmoglein 1
Paraneoplastic pemphigus	Desmoglein 3, desmoplakin 1, desmoplakin 2, BP230, envoplakin, periplakin, others
IgA pemphigus	Desmocollin 1

From Mutasim DF et al: *J Am Acad Dermatol* 45:803, 2001.
PMID: 11712024

Pemphigus Classification

- Deep forms of pemphigus:
- Pemphigus vulgaris
- Pemphigus vegetant
- Superficial forms of pemphigus:
- Pemphigus foliaceus
- Pemphigus erythematosus
- Endemic pemphigus (fogo selvageum)
- Paraneoplastic pemphigus
- Drug-Induced pemphigus

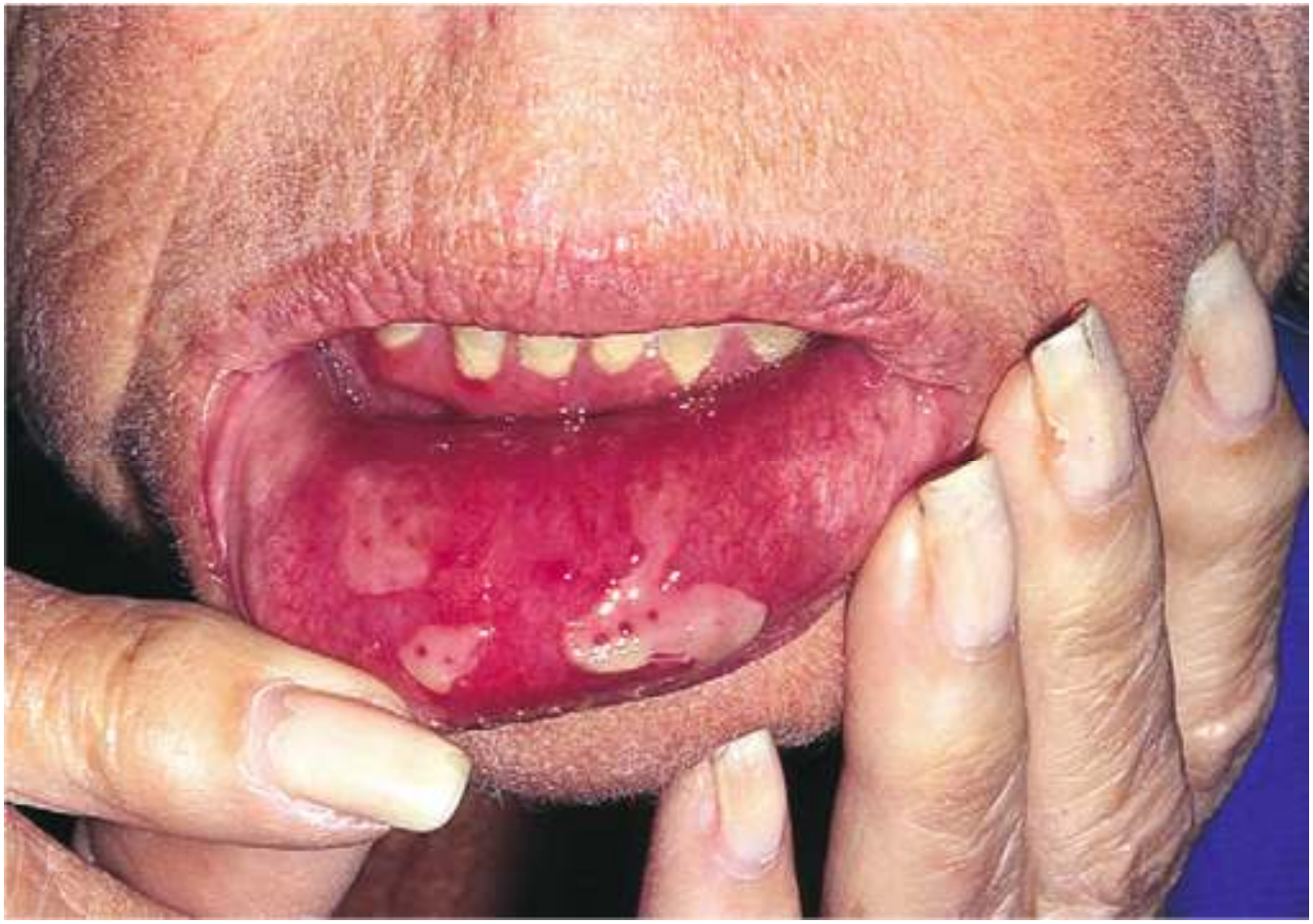
Pemphigus Vulgaris (PV)
History

- PV usually starts in the oral mucosa, and months may elapse before skin lesions occur
- Lesions may be localized for 6 to 12 months, after which generalized bullae occur
- No pruritus, but burning and pain
- Painful and tender mouth lesions may prevent adequate food intake
- Epistaxis, hoarseness, dysphagia
- Weakness, malaise, weight loss (with prolonged mouth involvement).

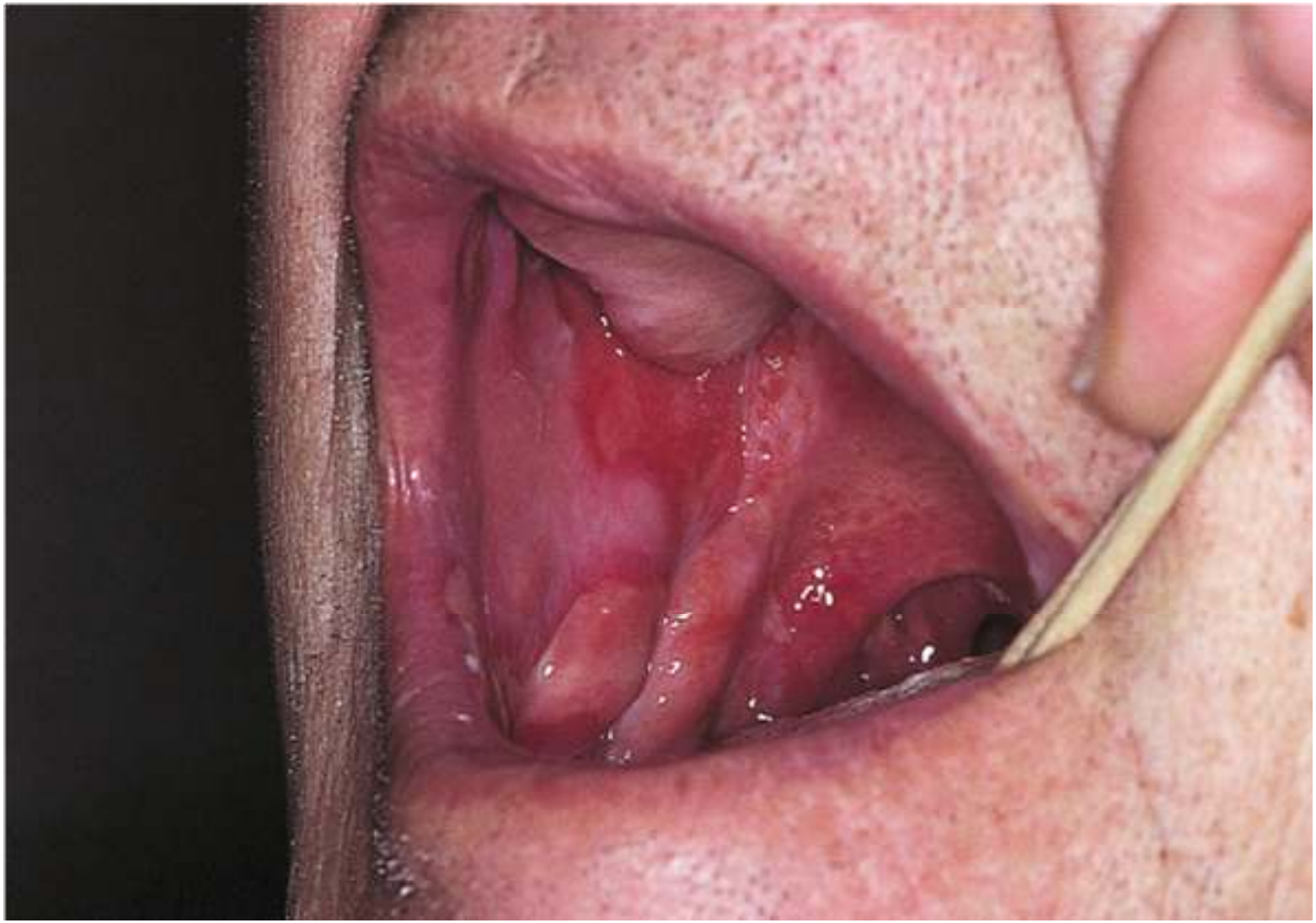
Physical examination

- Skin lesions: round or oval vesicles and bullae with serous content, flaccid, easily ruptured, and weeping, arising on normal skin, randomly scattered, discrete
- Localized to mouth or generalized with a random pattern
- Extensive erosions that bleed easily, crusts particularly on scalp
- Since blisters rupture so easily, only erosions are seen in many patients.

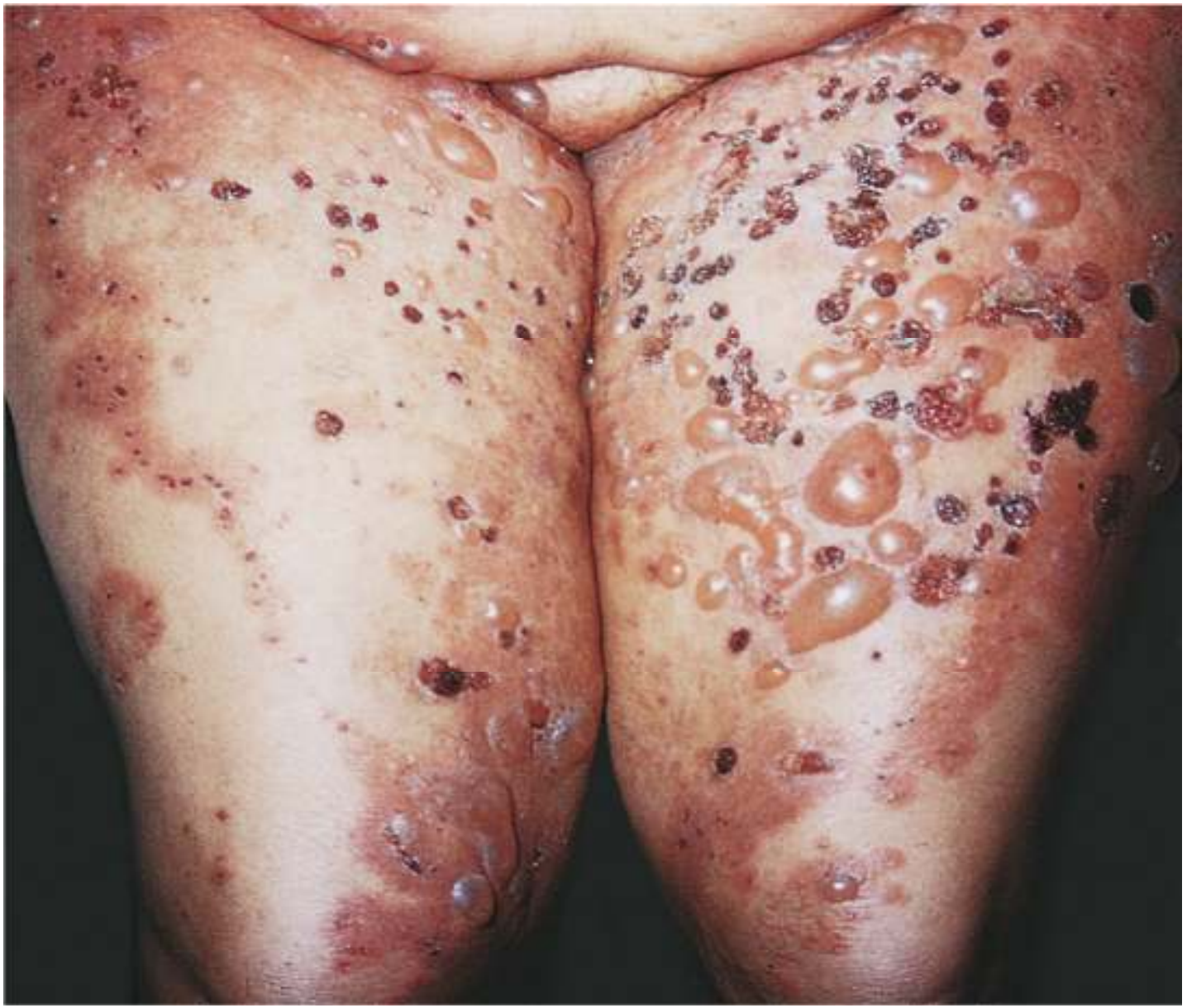
Pemphigus vulgaris: oral lesions

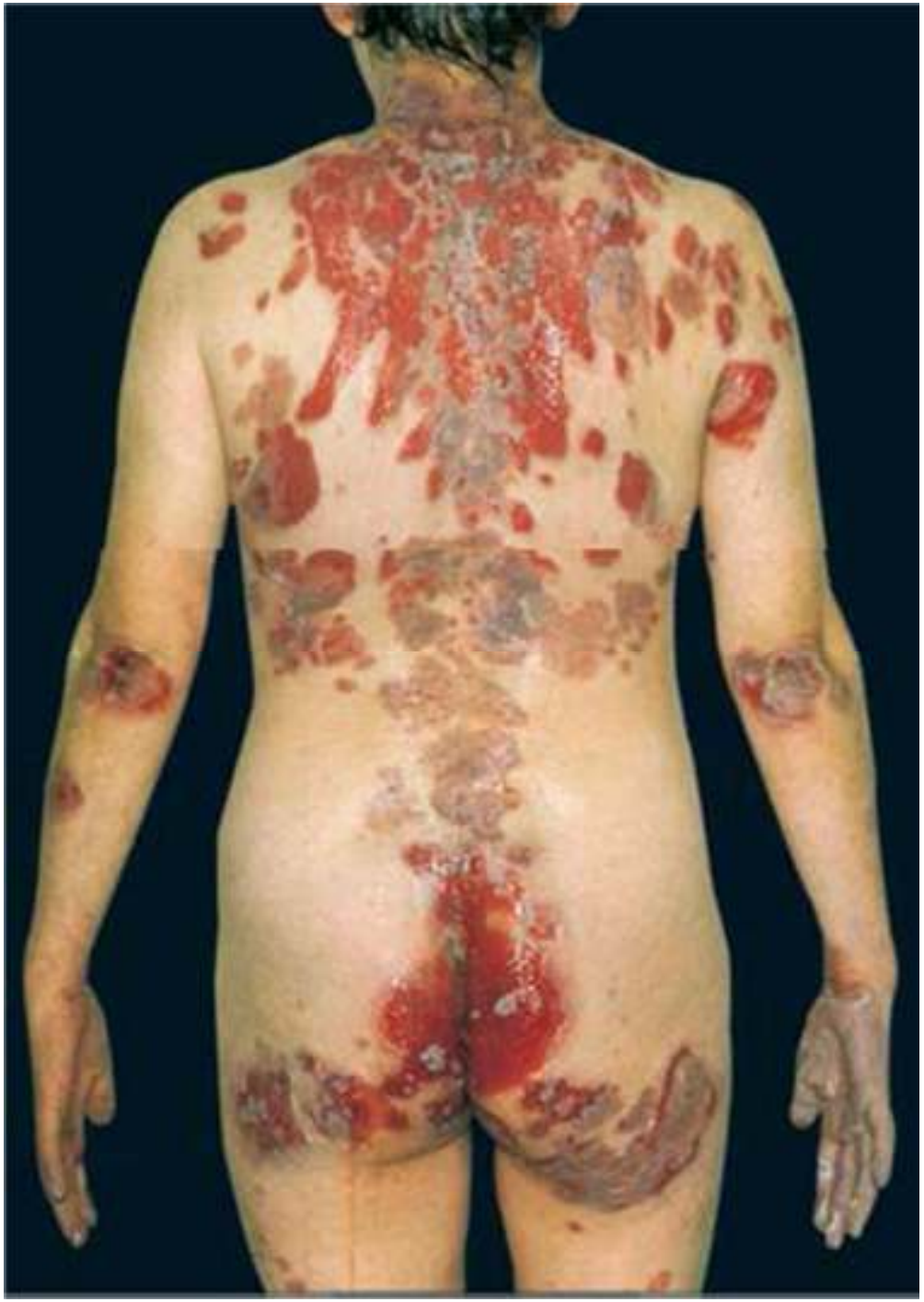


Pemphigus vulgaris: oral lesions



PV blistering, but without scarring



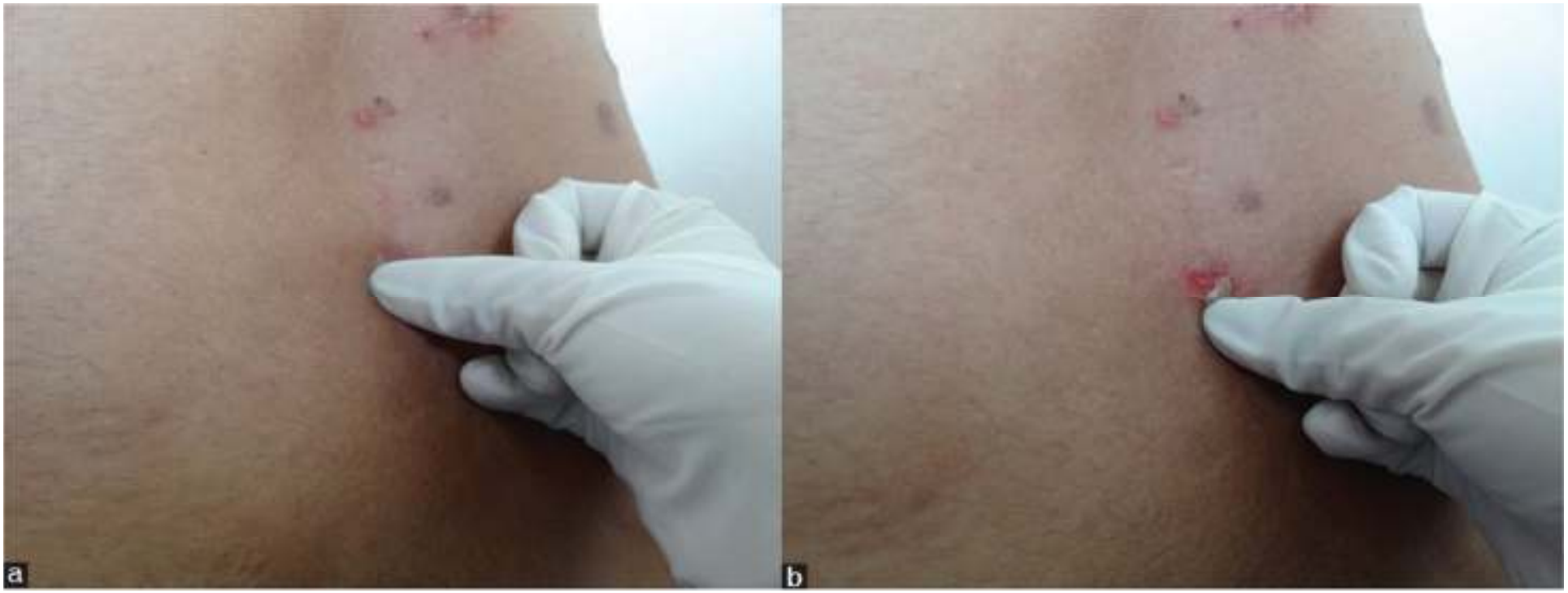


PV

Physical examination

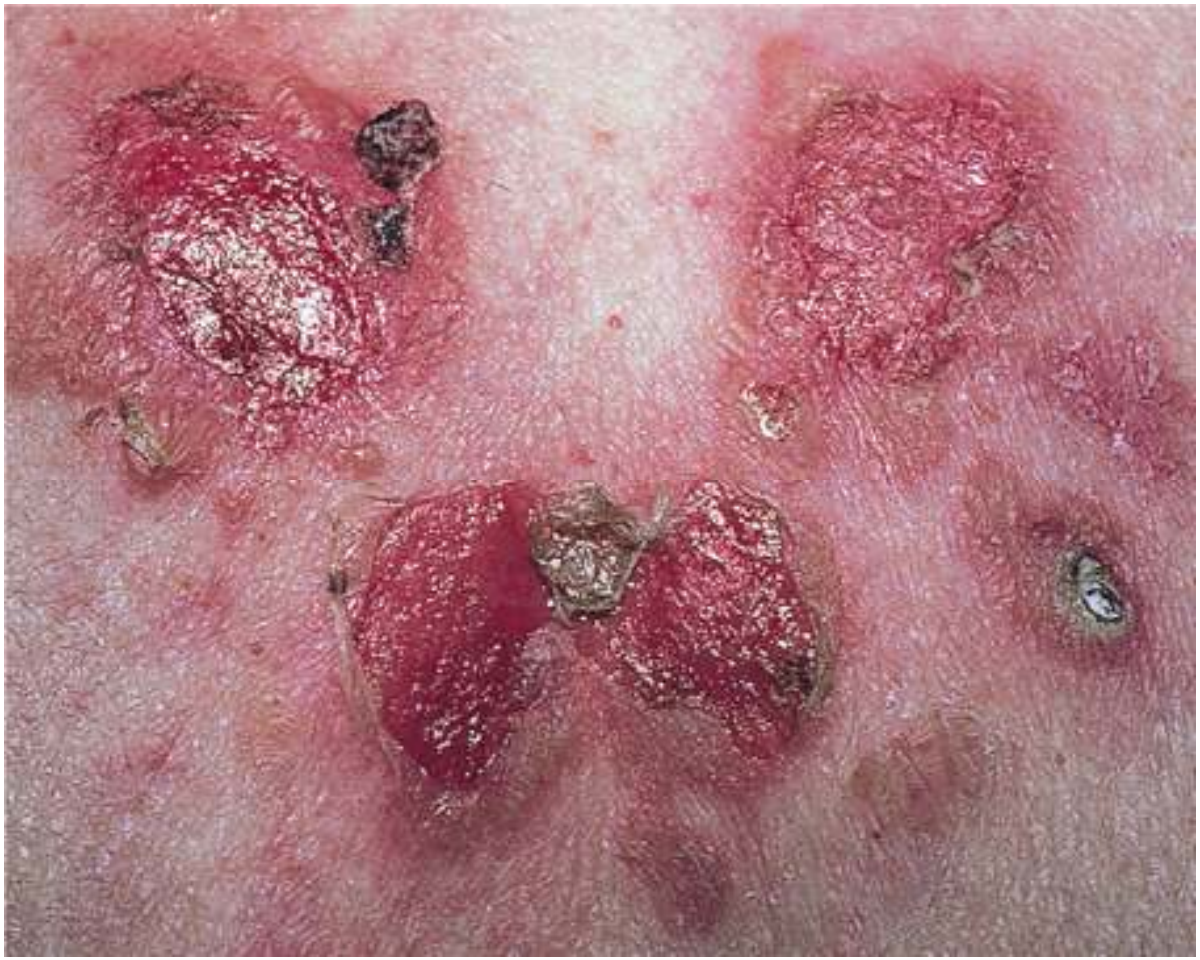
- Nikolsky's sign: dislodging of epidermis by lateral finger pressure in the vicinity of lesions, which leads to an erosion
- Asboe-Hansen sign: pressure on bulla leads to lateral extension of blister
- Pear sign: pear-like bulla in patient's vertical position
- Sites of predilection: scalp, face, chest, axillae, groin, umbilicus; extensive involvement of back in bed-ridden patients
- Mucous membranes: bullae rarely seen, erosions of mouth and nose, pharynx and larynx, vagina.

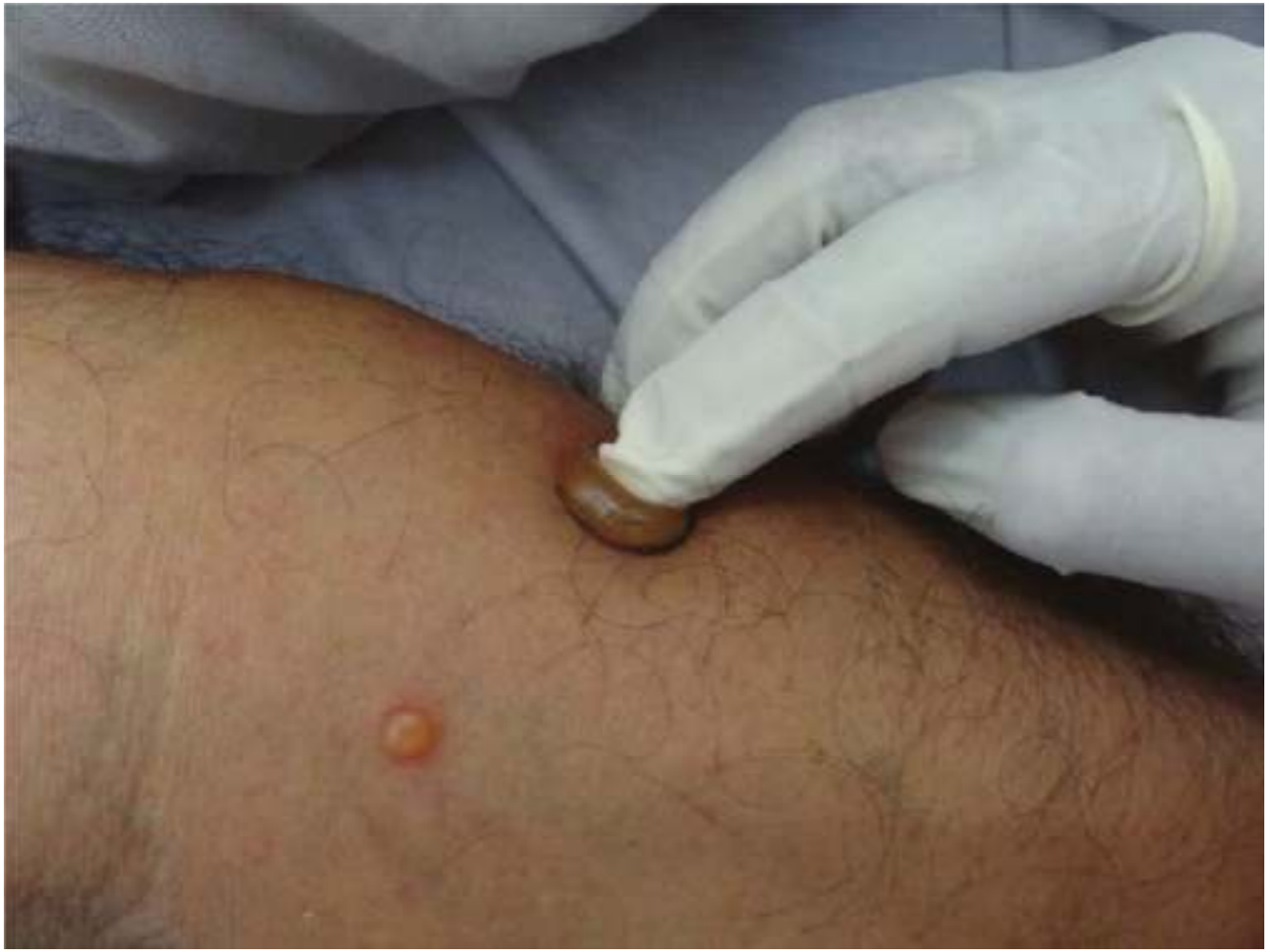
Nikolsky’s sign



The sign is elicited by applying tangential pressure with a finger or thumb to the affected skin (1), peri-lesional skin (2), or normal skin (3) in patients with suspected pemphigus. It is termed positive if there is extension of the blister and/or removal of epidermis in the rubbed area (1). "Marginal Nikolsky's sign" describes the extension of the erosion on the surrounding normal-appearing skin by rubbing the skin surrounding existing lesions (2), while "Direct Nikolsky's sign" is the induction of an erosion on normal-appearing skin, distant from the lesions (3).

PV: Nikolsky’s sign





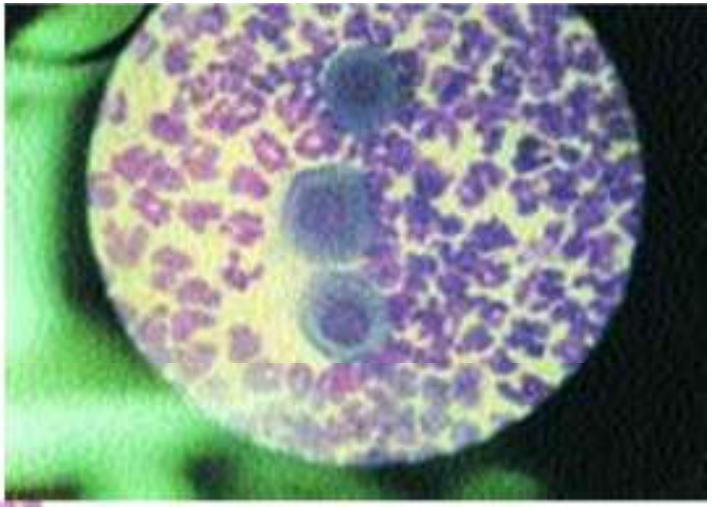
Bulla spread sign (Asboe-Hansen sign)

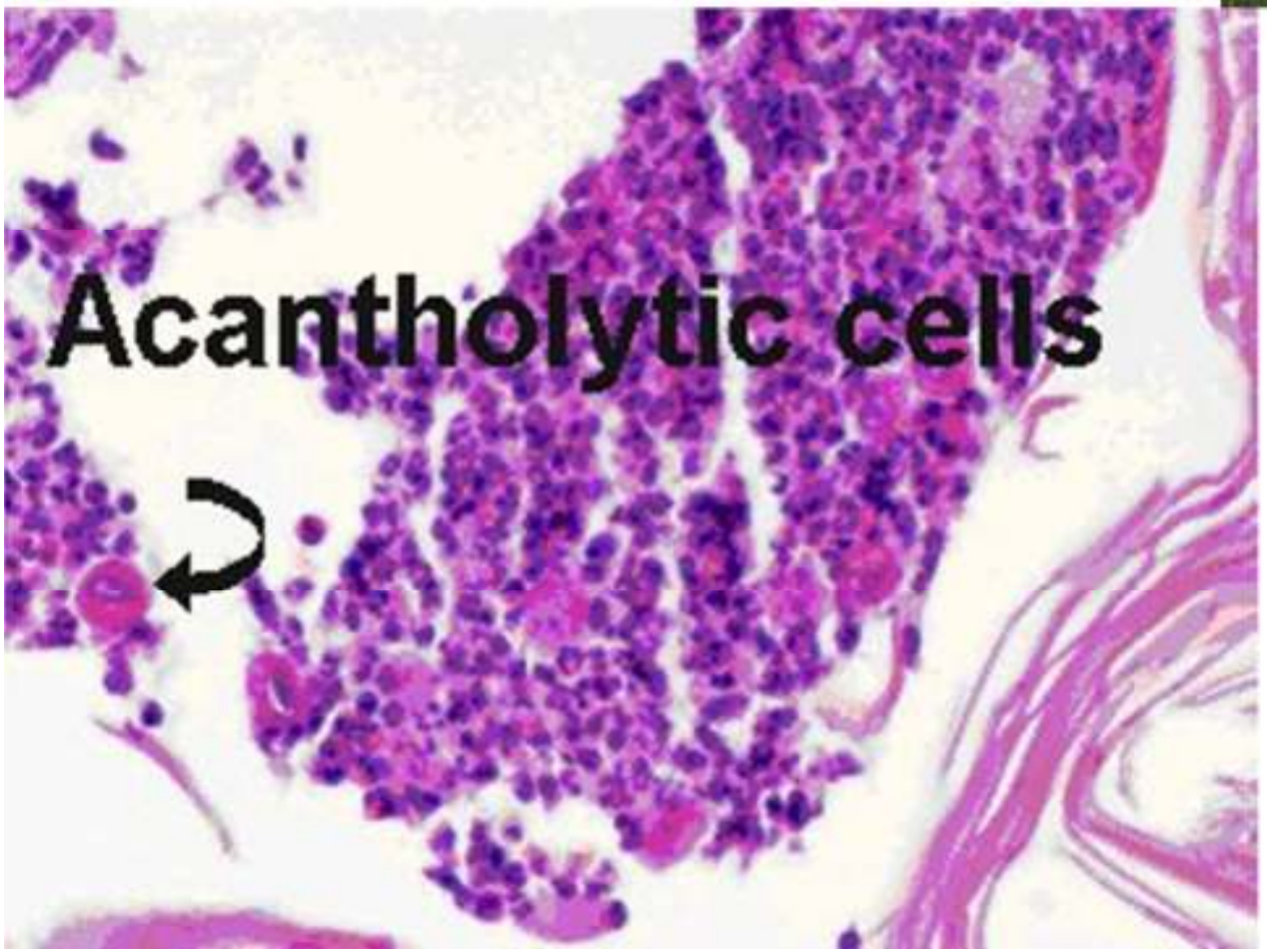
It is the enlargement of an intact blister by the application of mechanical pressure on its roof. If one carefully presses upon the blister, it enlarges towards its periphery due to the mechanical pressure of the blister fluid. In PV, the blister extension has a sharp angle, whereas in BP, the advanced border is rounded.

Laboratory Examinations

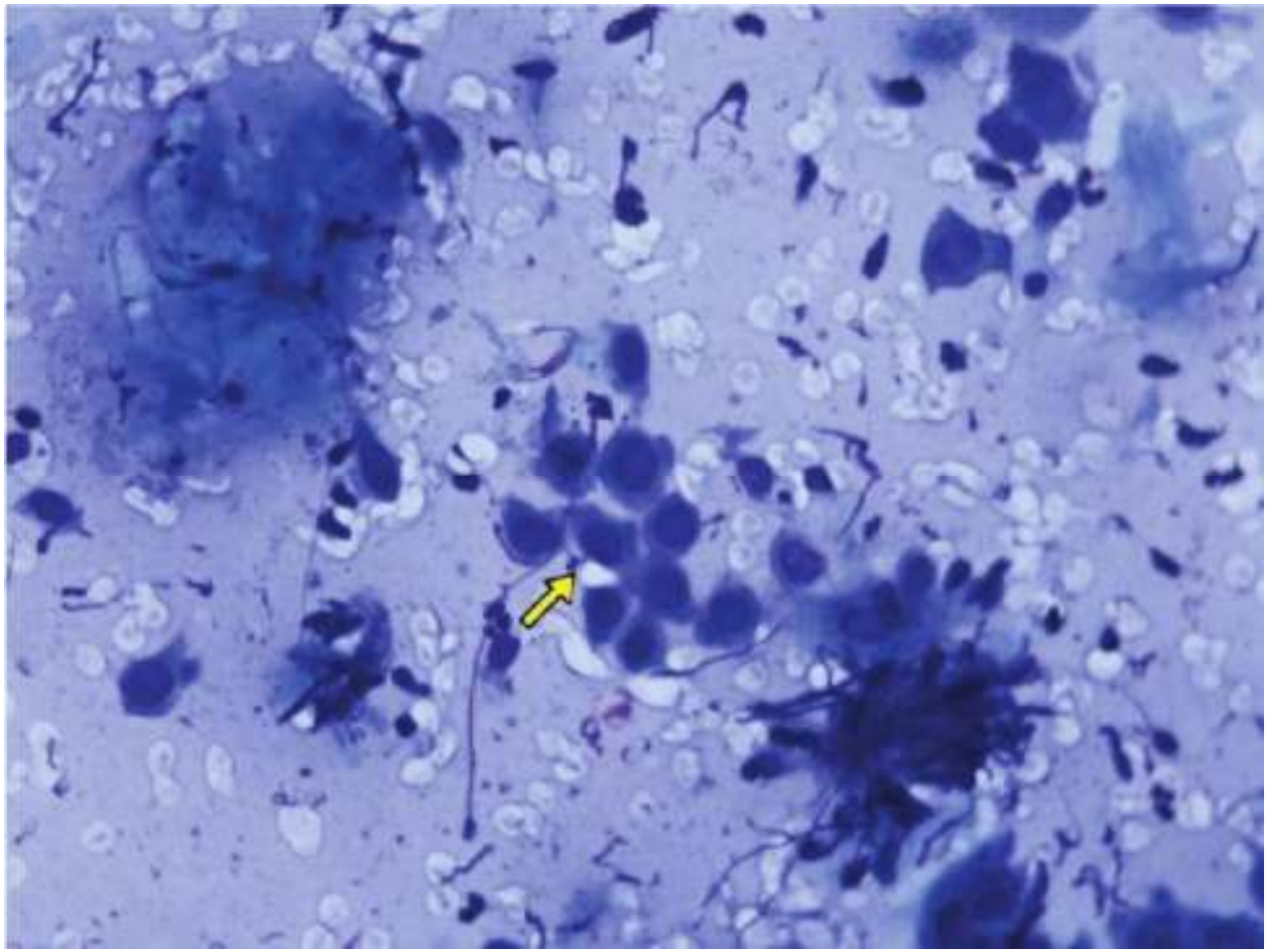
- Pemphigus cytology – Tzank smear – acantholytic cells.
- PV dermatopathology (histopathology) in light microscopy:
  - (1) loss of intercellular cohesion in lower part of epidermis, leading to
  - (2) acantholysis (separation of keratinocytes) and to
  - (3) bulla that is split just above the basal cell layer and contains separated, smaller, rounded-up keratinocytes, so-called acantholythic cells.

Pemphigus cytology

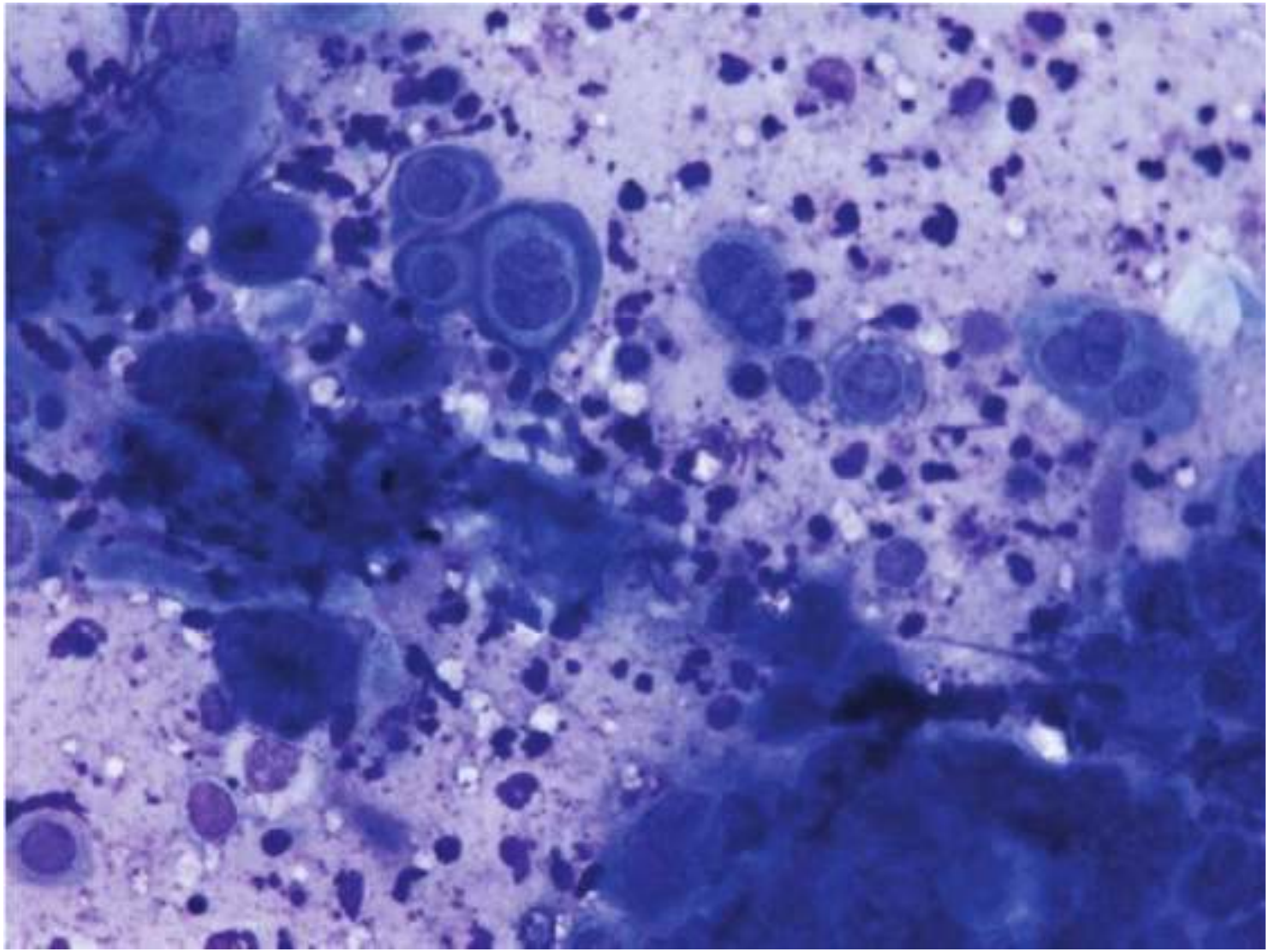




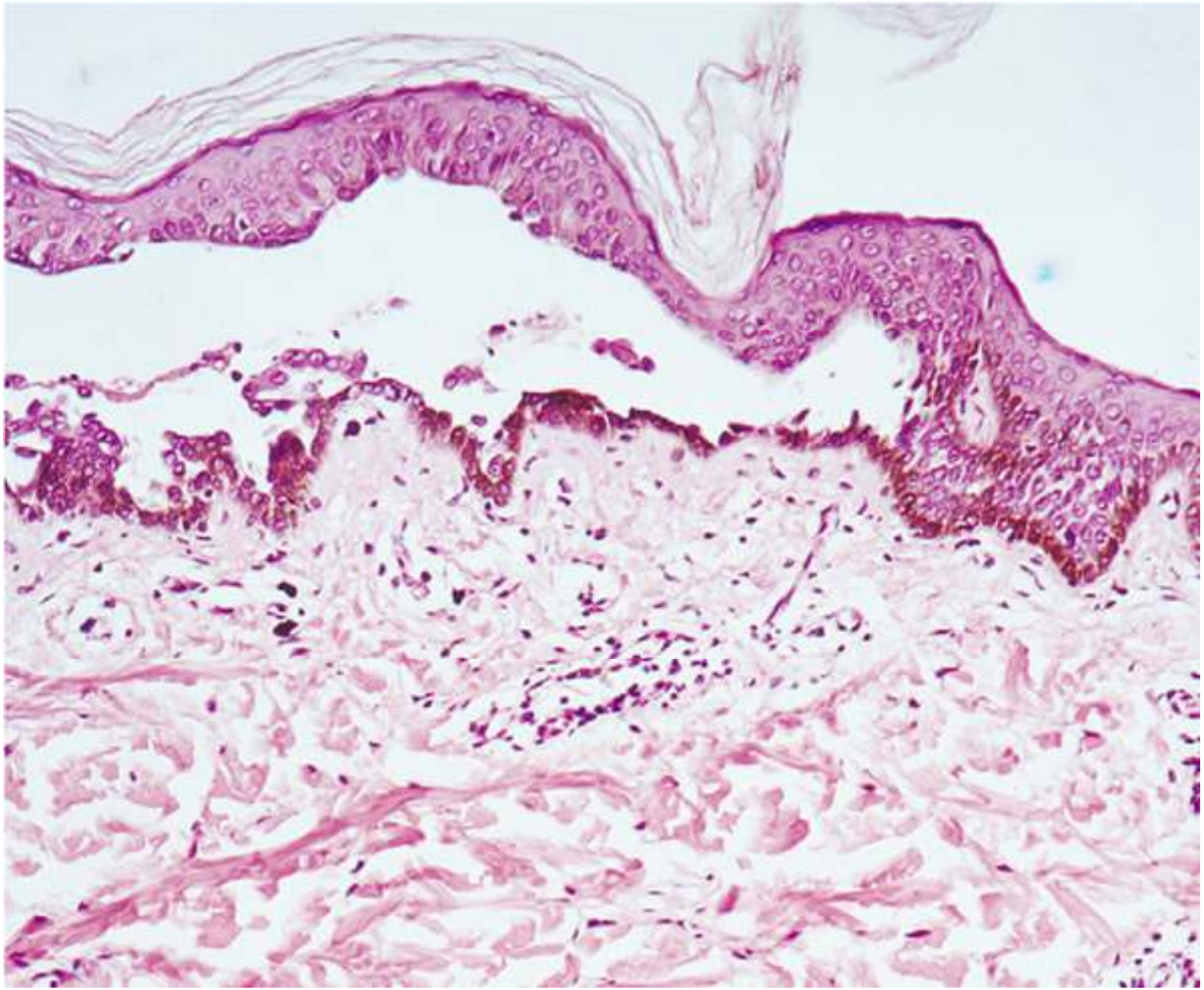
Acantholytic cells



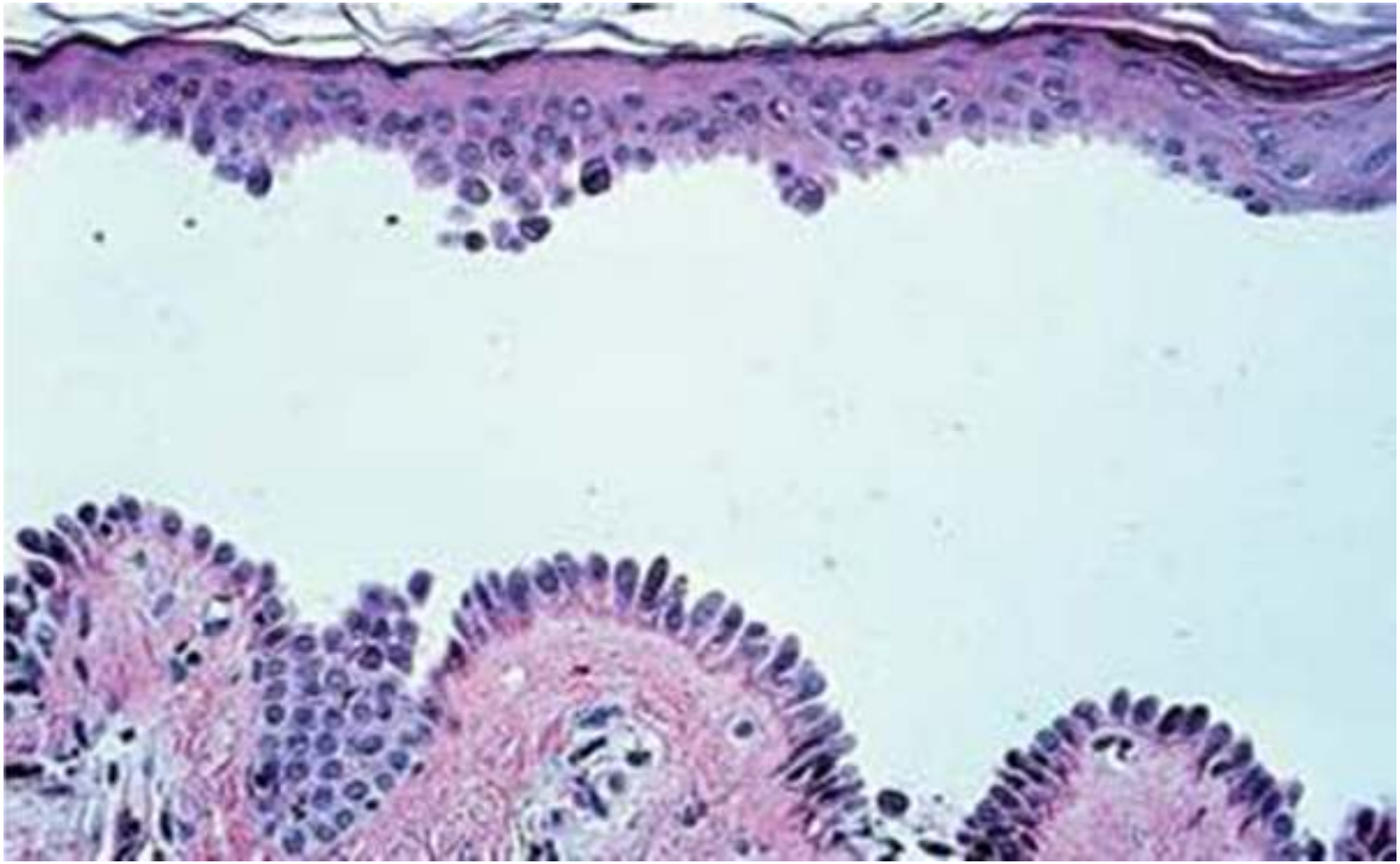
Tzank cells in herpes simplex



PV histopathology



PV histopathology:
the row of tombstones



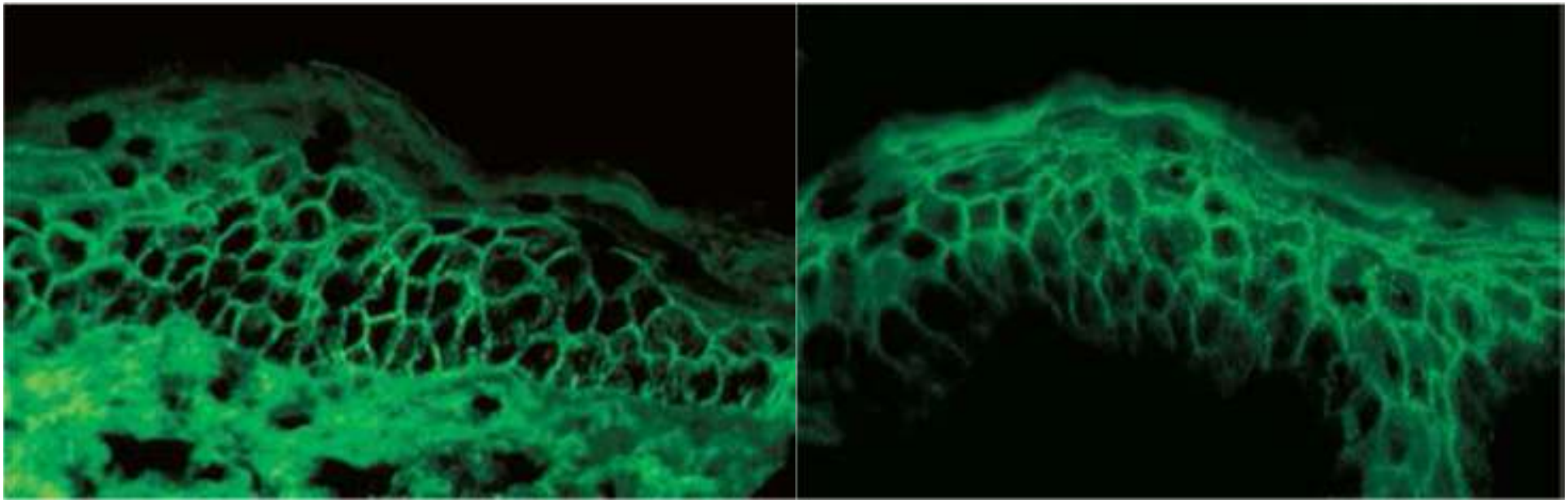
Laboratory Examinations

PV immunofluorescence (IF)

- direct IF staining reveals IgG and often C3 deposited in lesional and paralesional skin in the intercellular substance of the epidermis
- indirect IF detects serum circulating autoantibodies (IgG) of anti-desmoglein 3. Titer usually correlates with activity of disease process.

Immunofluorescence in pemphigus: epidermis

PV **PF**



Course

- The disease inexorably progresses to death unless treated aggressively with immunosuppressive drugs.

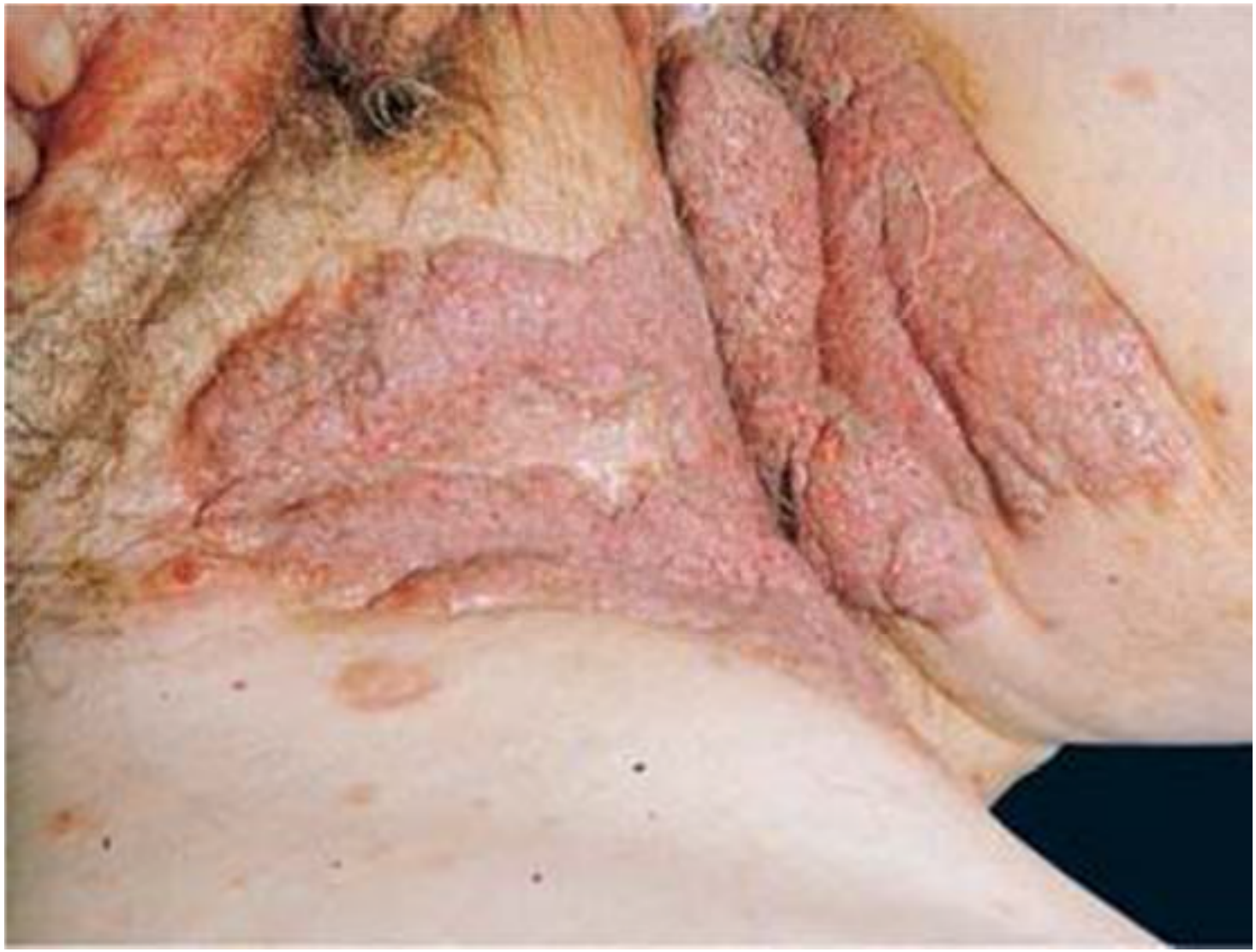
- The mortality rate has been markedly reduced since treatment has become available.

Other Variants:
Pemphigus Vegetant (PVeg)

- Usually confined to intertriginous regions, perioral area, neck and scalp;
- Granulomatous vegetating purulent plaques that extend centrifugally;
- Suprabasal acantholysis with intraepidermal abscesses containing mostly eosinophils, epidermis hyperplasia and granulation tissue
- IgG autoantibodies as in PV;
- PV may evolve into PVeg and vice versa.

Pemphigus vegetans

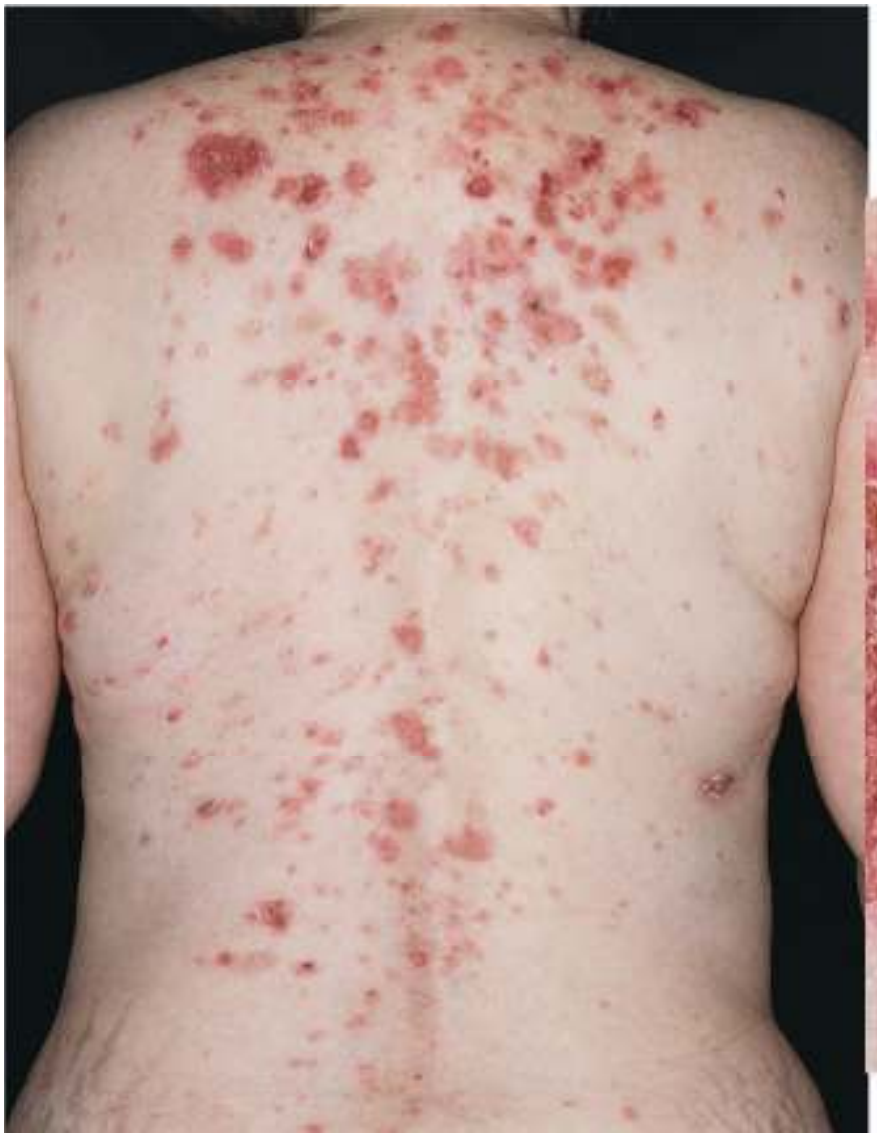
Pemphigus vegetans

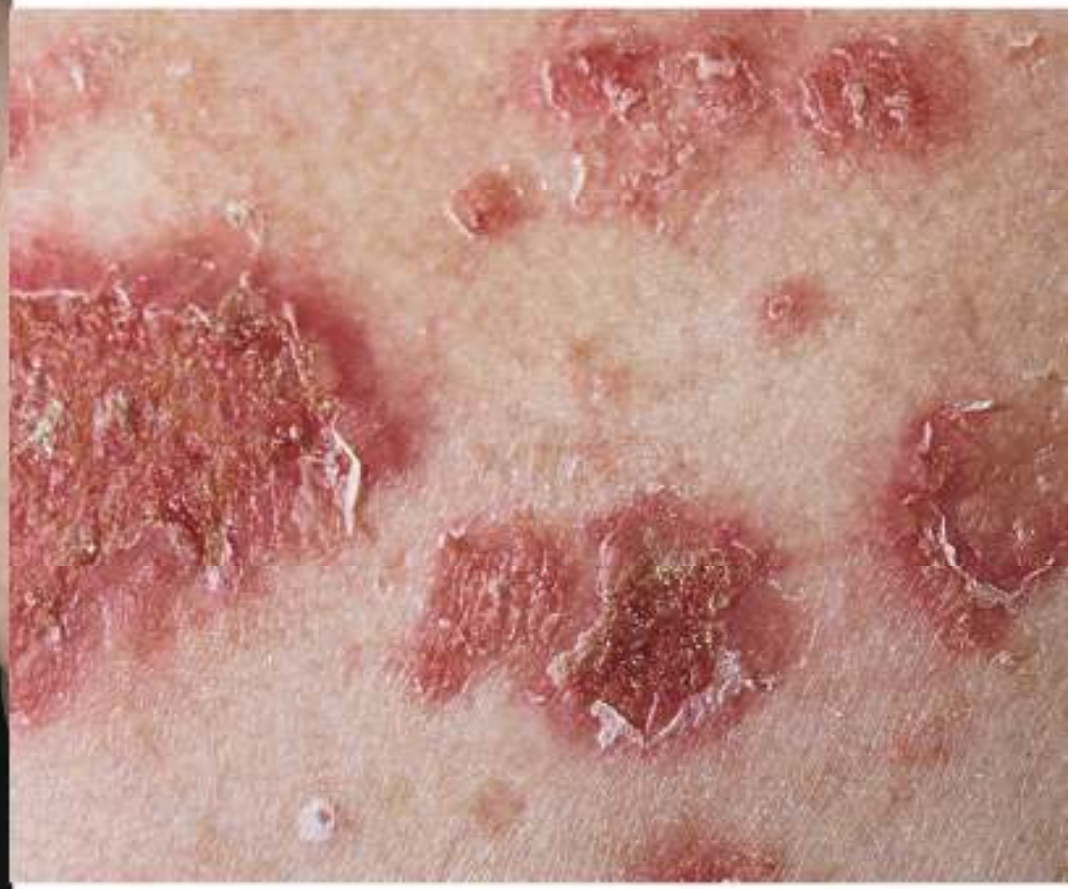


Other Variants:
Pemphigus Foliaceus (PF)

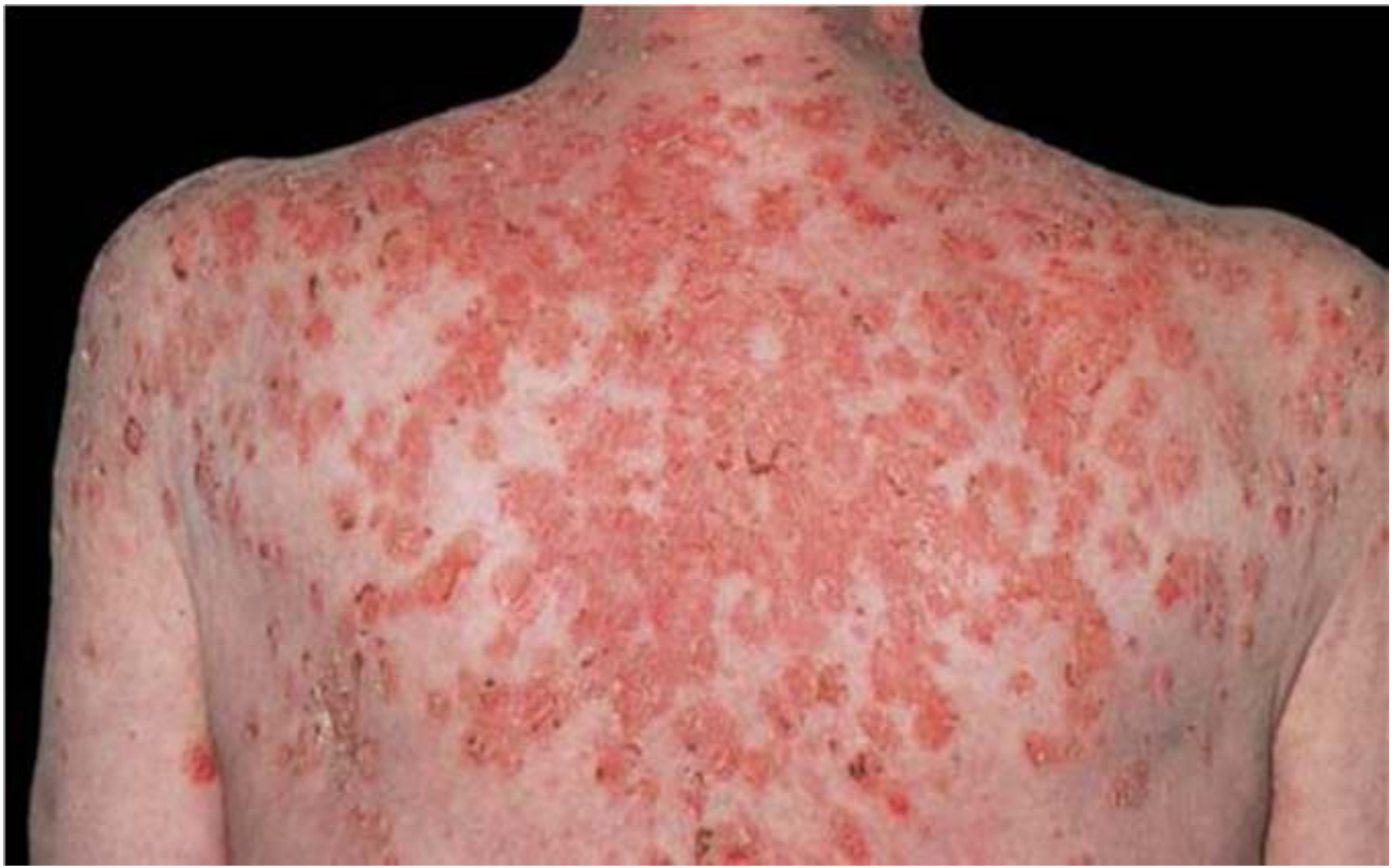
- Most commonly on face, scalp, upper chest, and abdomen, but may involve the entire skin, presenting as exfoliative erythroderma
- Superficial form of pemphigus with acantholysis in the granular layer of the epidermis
- Bullae hardly ever present, lesions consist of erythematous patches and erosions covered with crusts
- PF is mediated by circulating autoantibodies to desmoglein 1, which is a superficial intercellular antigen in the desmosomes of keratinocytes.
- That explains the different sites of acantholysis (in the granular layer) and thus the different clinical appearances from PV without mucous membranes involvement.

Pemphigus foliaceus

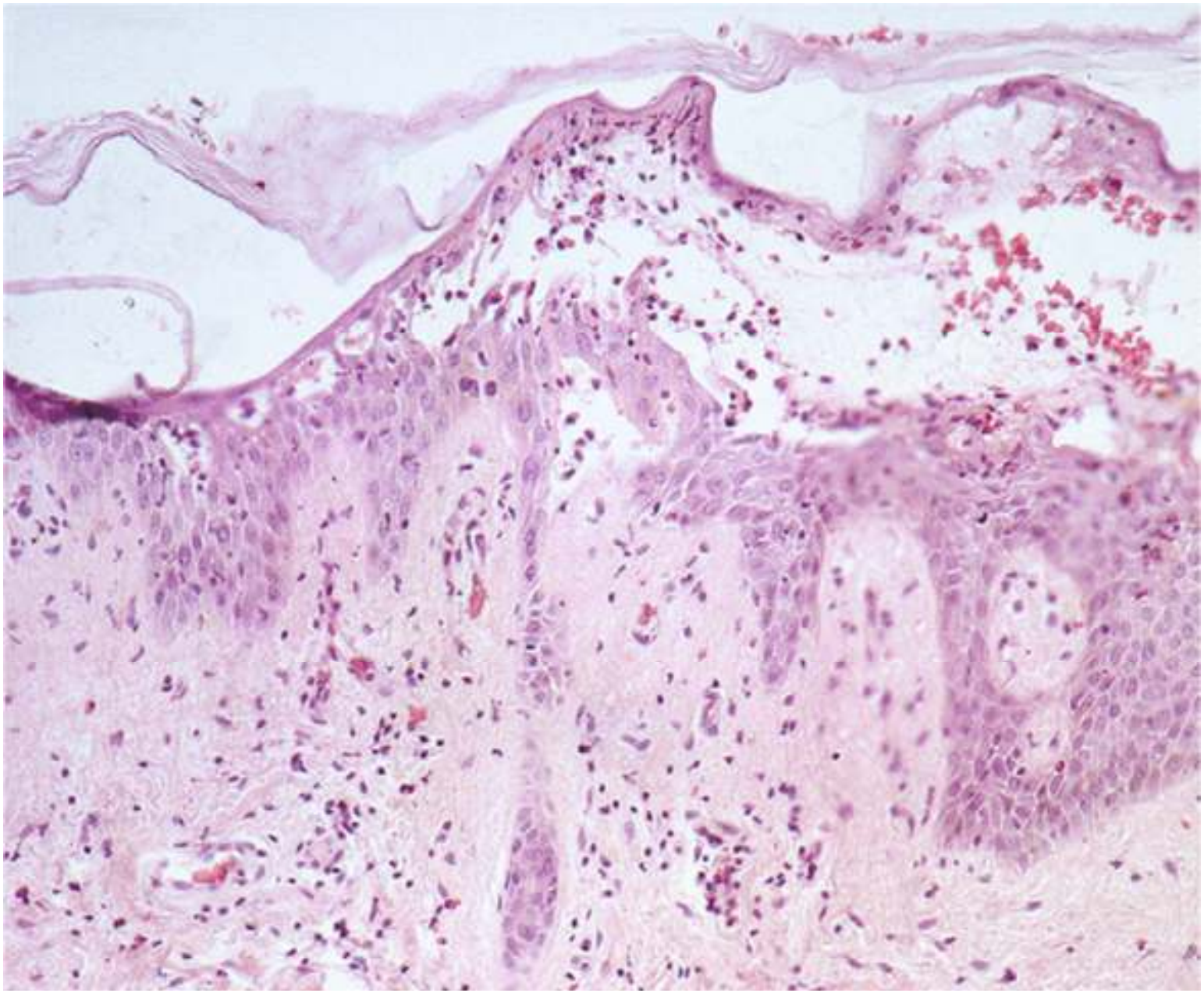




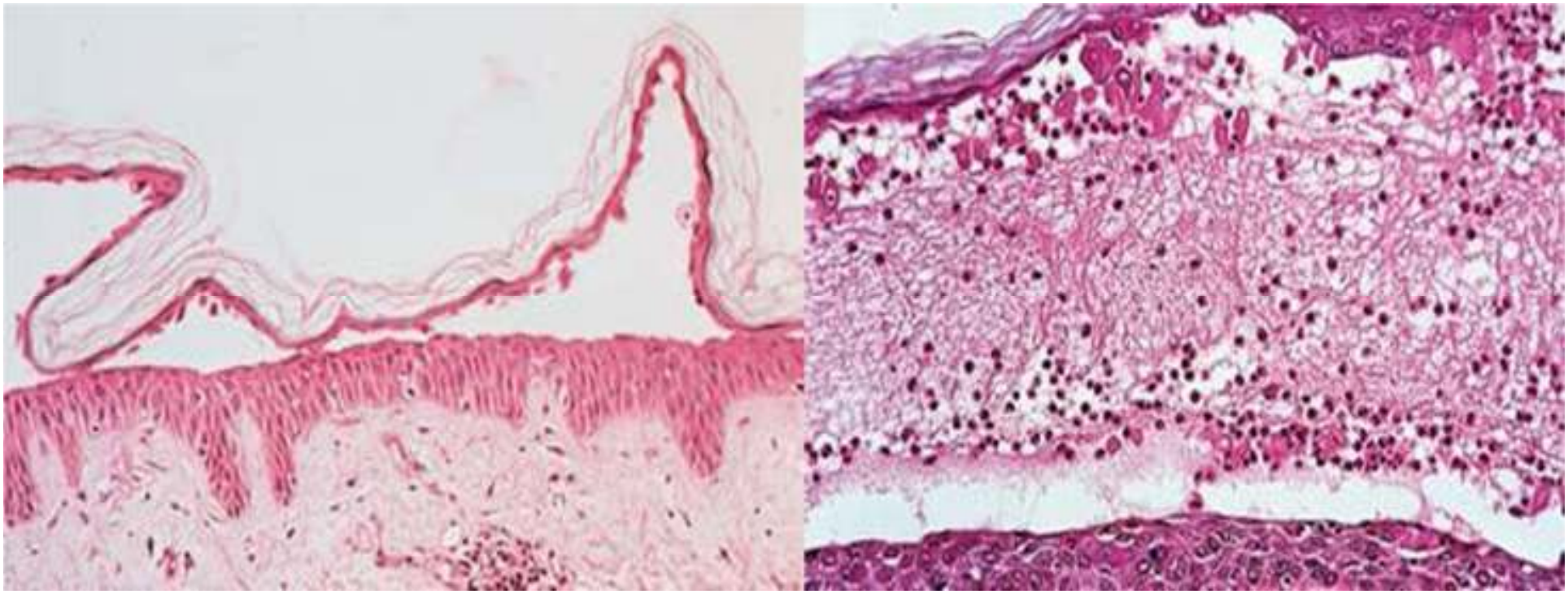
Pemphigus foliaceus



PF histopathology



Histopathology of pemphigus foliaceus



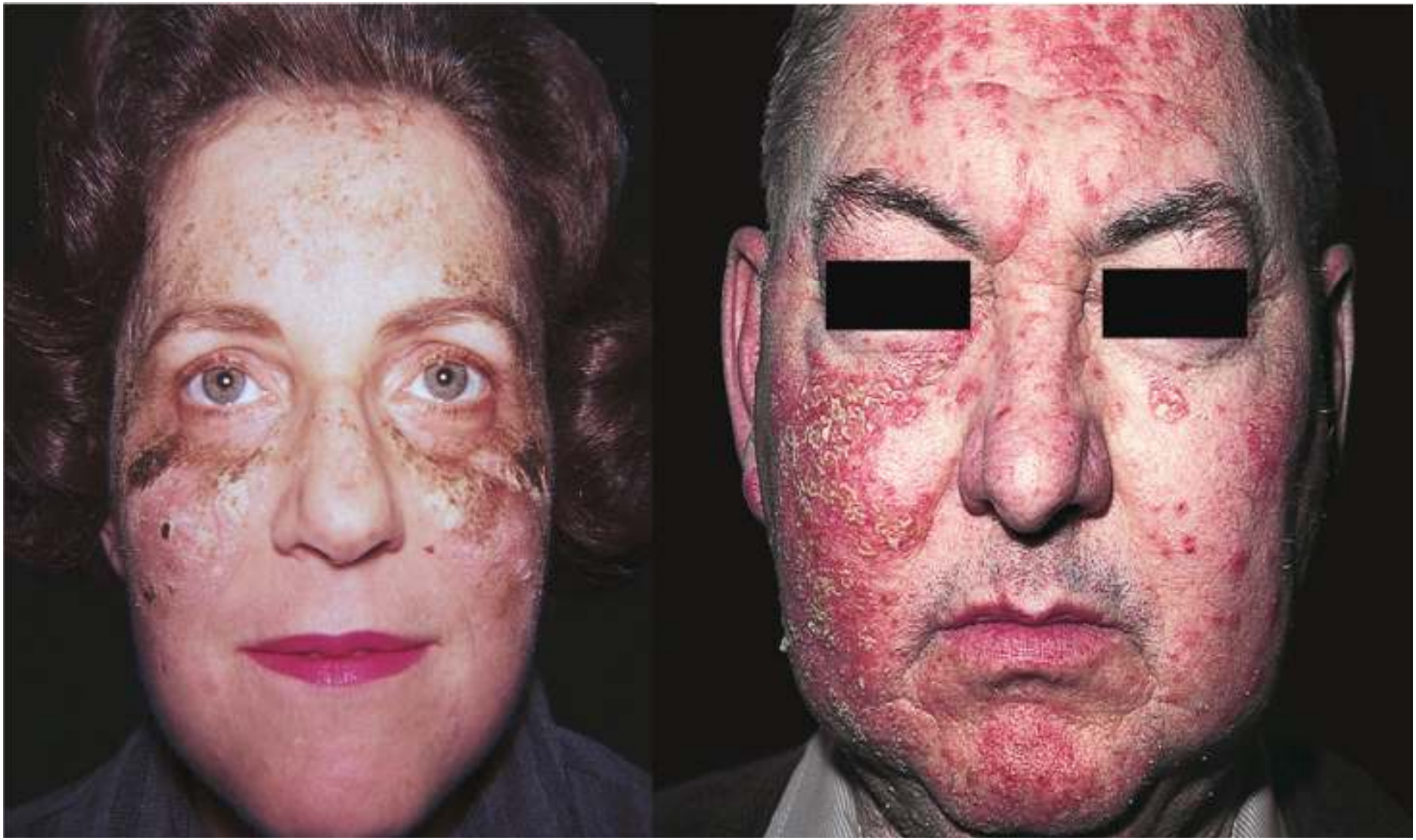
Other Variants:
Brazilian Pemphigus (Fogo Selvagum)

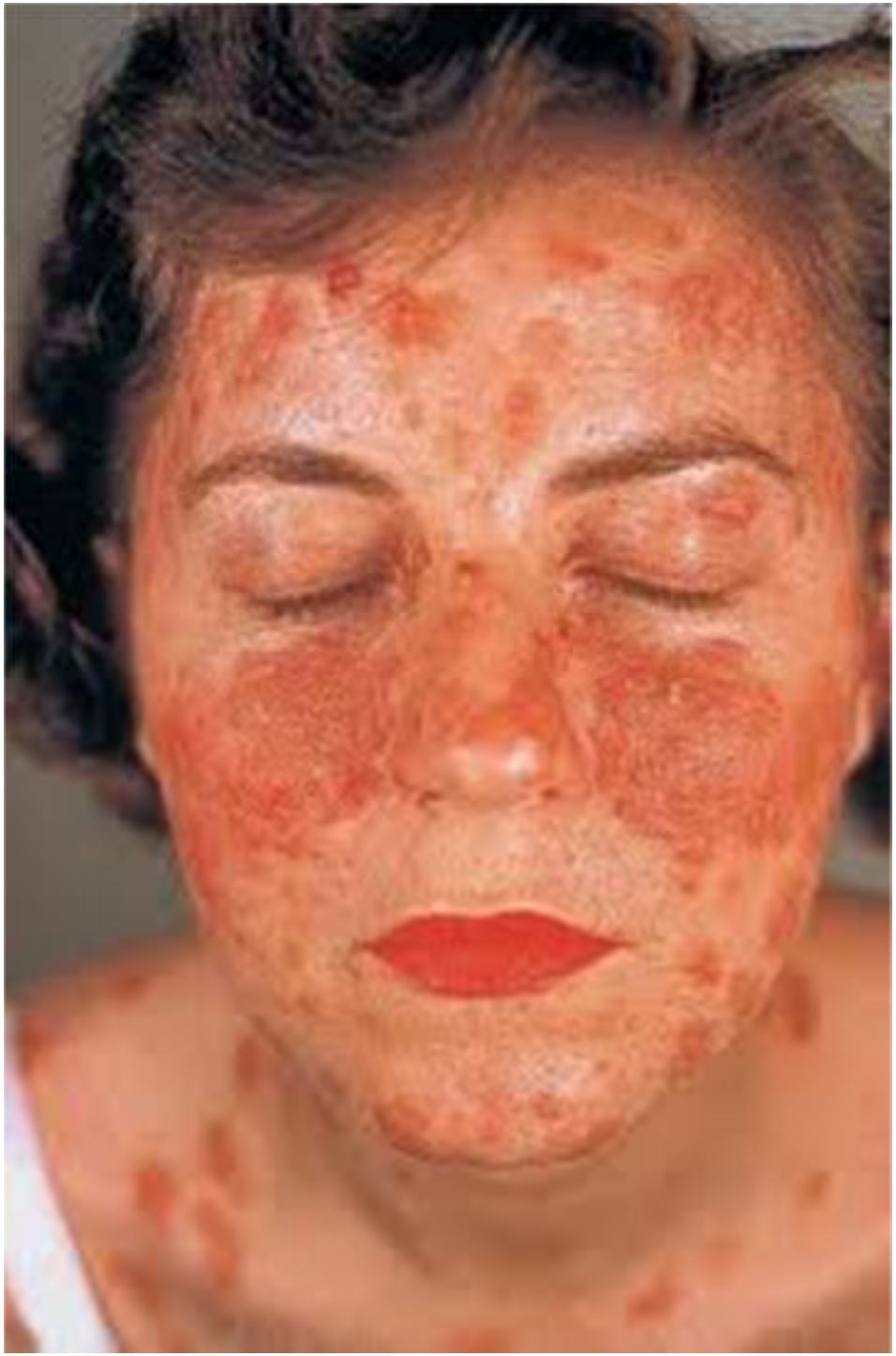
- *Fogo Selvagum* is a Brazilian variant of pemphigus foliaceus, it is also called endemic pemphigus
- *Fogo selvagum* may be associated with the black fly, Simulium pruinosum
- Clinically, histologically, and immunopathologically identical to pemphigus foliaceus
- More than 1000 new cases per year are estimated to occur in the endemic regions.

Other Variants:
Pemphigus Erythematosus (PE)

- Also called Senear-Usher syndrome
- A localized variety of pemphigus foliaceus largely confined to seborrheic sites
- Erythematous, crusted, and erosive lesions in the “butterfly” area of the face, forehead, presternal, and interscapular regions
- There are immunoglobulin and complement deposits at the dermal-epidermal junction and positive antinuclear antibodies (as in case of lupus erythematosus), in addition to typical intercellular pemphigus antibodies (as in case of pemphigus foliaceus).

Pemphigus erythematosus (Senear-Usher syndrome)

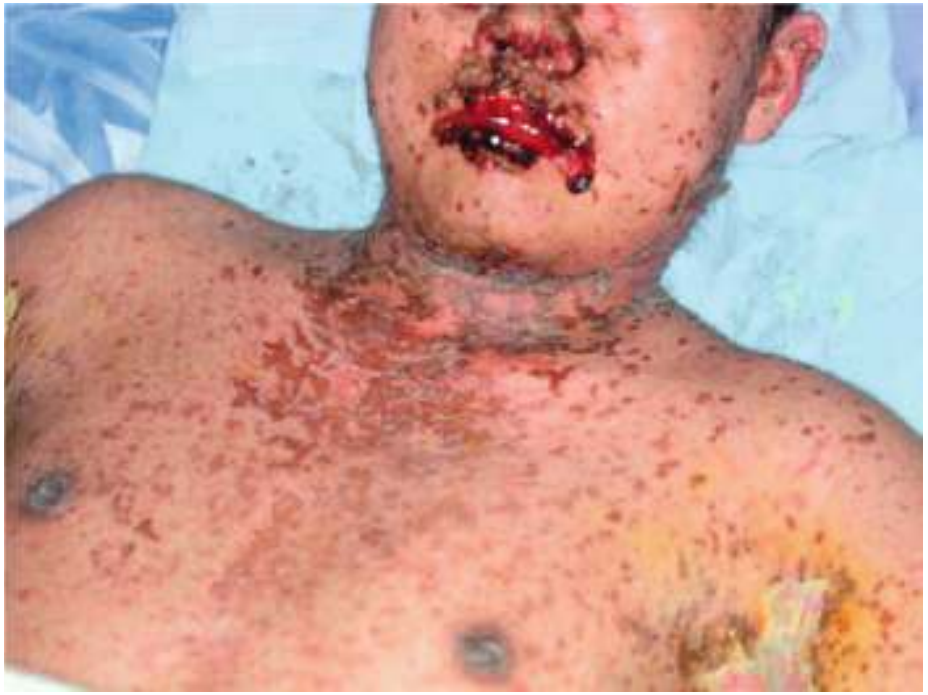




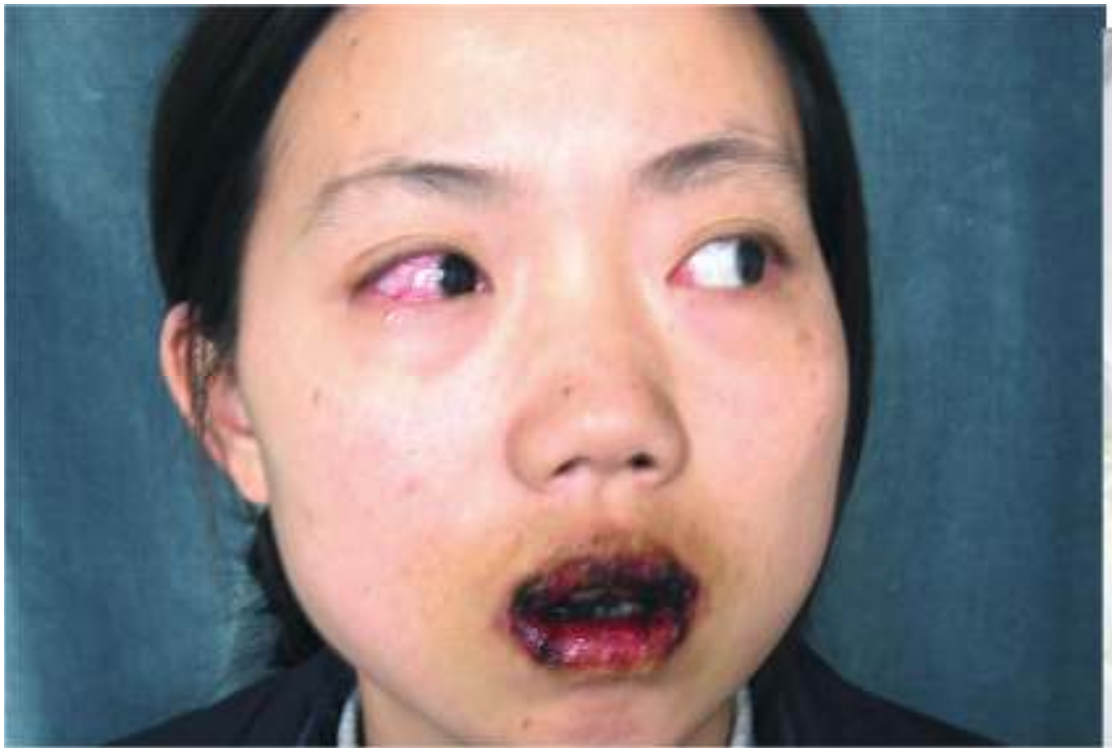
Pemphigus erythematosus (Senear-Usher syndrome)

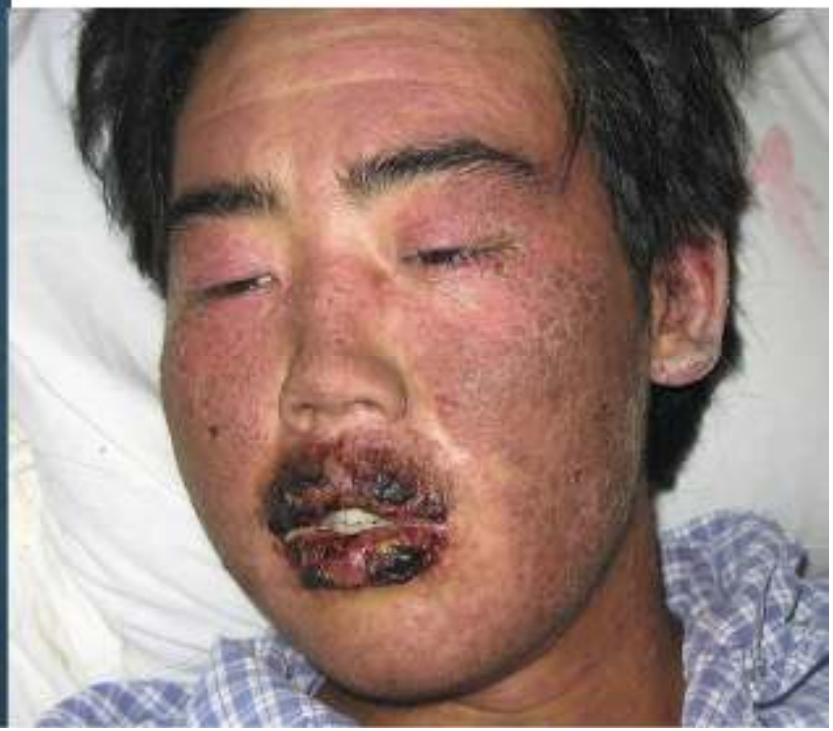
Other Variants:
Paraneoplastic Pemphigus

- Mucous membranes primarily and most severely involved
- Lesions combine features of pemphigus vulgaris and erythema multiforme, clinically and histologically.
- Usually associated with lymphoma, thymoma, less commonly with sarcoma/other tumors
- Usually recalcitrant to therapy



Paraneoplastic pemphigus



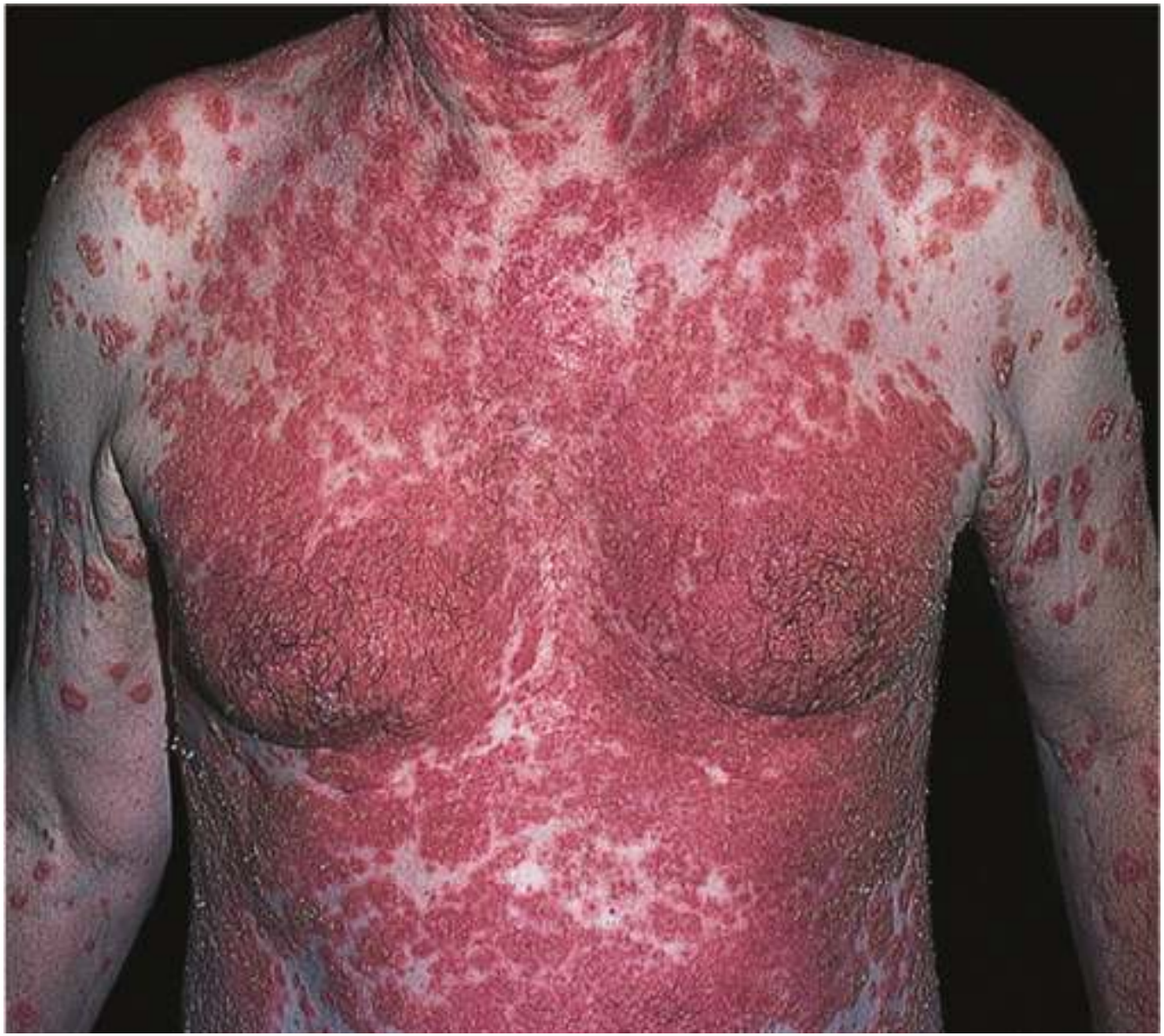


Other Variants:
Drug-Induced Pemphigus

- A pemphigus vulgaris or foliaceus – like syndrome can be induced by D-penicilamine and less frequently by captopril and other similar drugs.

- In most, but not all, instances the eruption resolves after termination of therapy with the offending drug.

Drug induced pemphigus: penicillamine (thiol drugs as PF; non-thiol drugs as PV)



Differential Diagnosis of Pemphigus

PEMPHIGUS SUBTYPES

- Pemphigus vulgaris
  - Pemphigus vegetans
- Pemphigus foliaceus
  - Pemphigus erythematosus
  - Endemic pemphigus foliaceus (e.g., fogo selvagem)
- Immunoglobulin A (IgA) pemphigus
  - Subcorneal pustular dermatosis
  - Intraepidermal neutrophilic dermatosis
- Paraneoplastic pemphigus

INTRAEPIDERMAL BLISTERING DISEASES WITHOUT AUTOANTIBODIES

- Familial benign pemphigus (Hailey-Hailey disease)
- Bullous impetigo, staphylococcal scalded-skin syndrome
- Blisters from herpes simplex and zoster
- Allergic contact dermatitis (e.g., rhus dermatitis)
- Epidermolysis bullosa simplex
- Incontinentia pigmenti

MOUTH ULCERS/EROSION WITHOUT AUTOANTIBODIES

- Aphthous ulcers
- Candidiasis
- Lichen planus
- Behçet disease

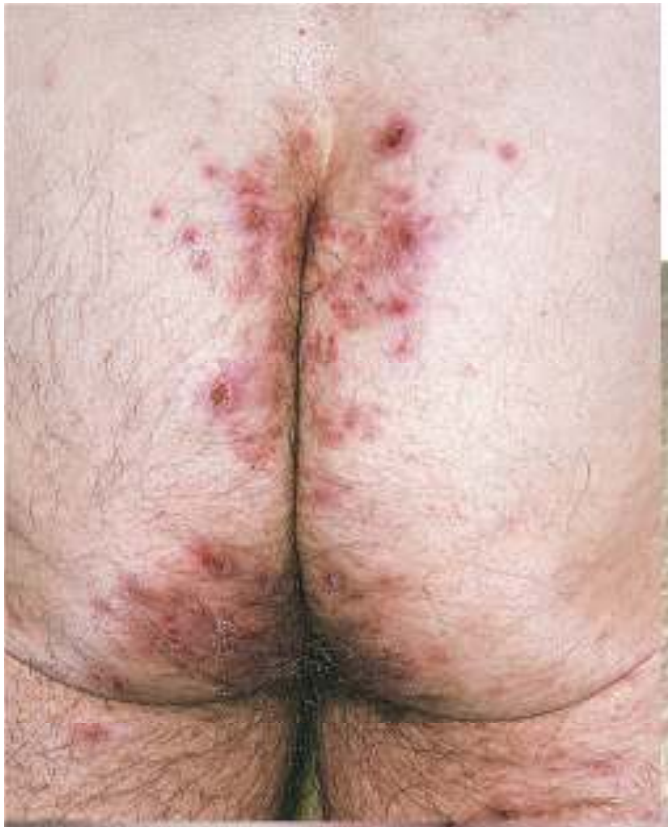
SUB-EPIDERMAL BLISTERING DISEASES WITH AUTOANTIBODIES

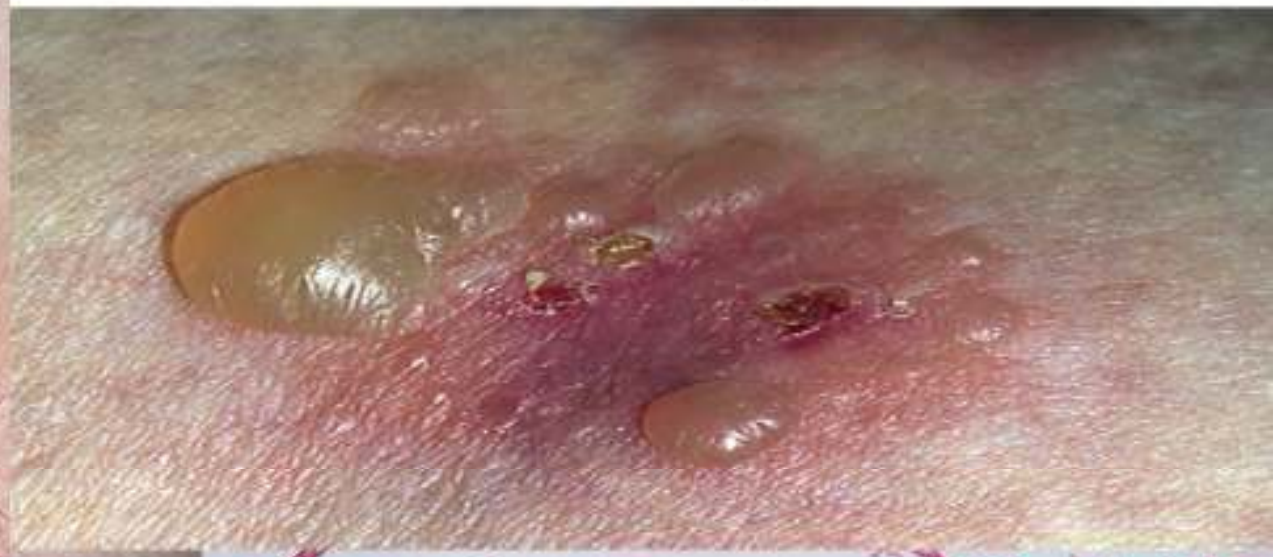
- Bullous pemphigoid
- Herpes gestationis
- Cicatricial pemphigoid
- Epidermolysis bullosa acquisita
- Linear IgA disease and chronic bullous disease of childhood
- Dermatitis herpetiformis
- Bullous lupus erythematosus

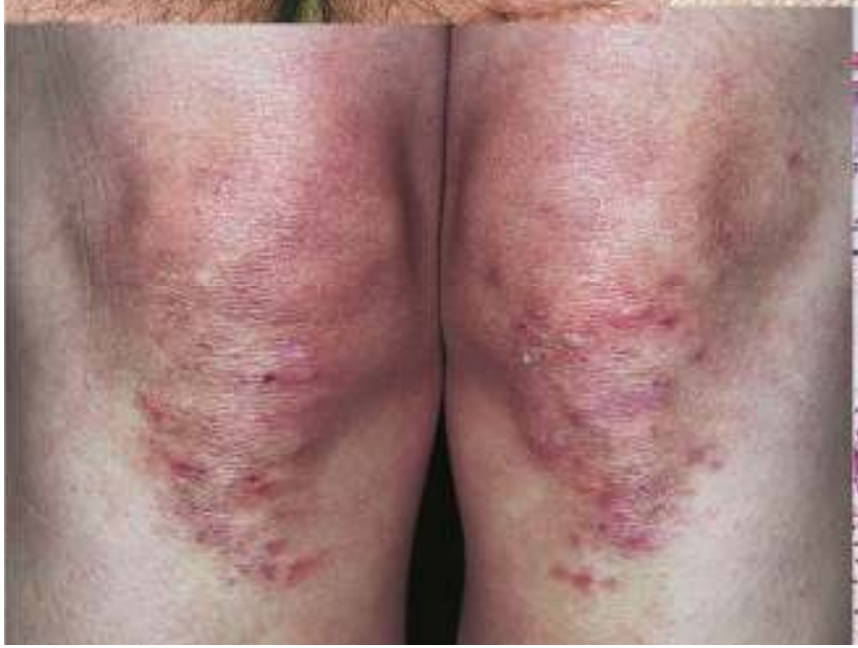
SUB-EPIDERMAL BLISTERING DISEASES WITHOUT AUTOANTIBODIES

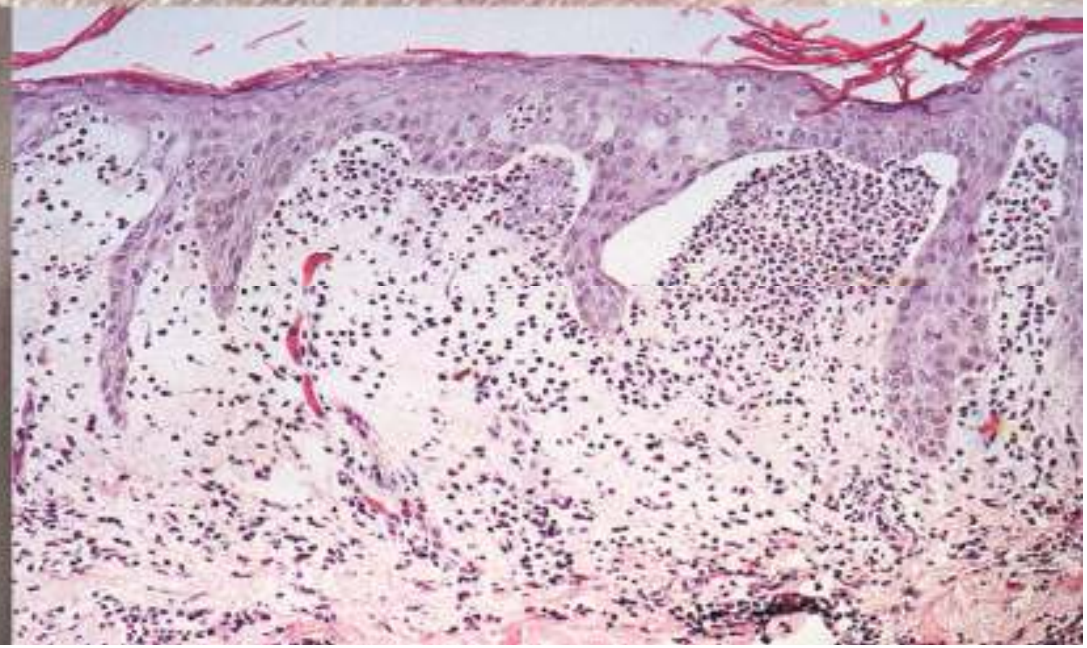
- Erythema multiforme
- Toxic epidermal necrolysis
- Porphyria
- Epidermolysis bullosa

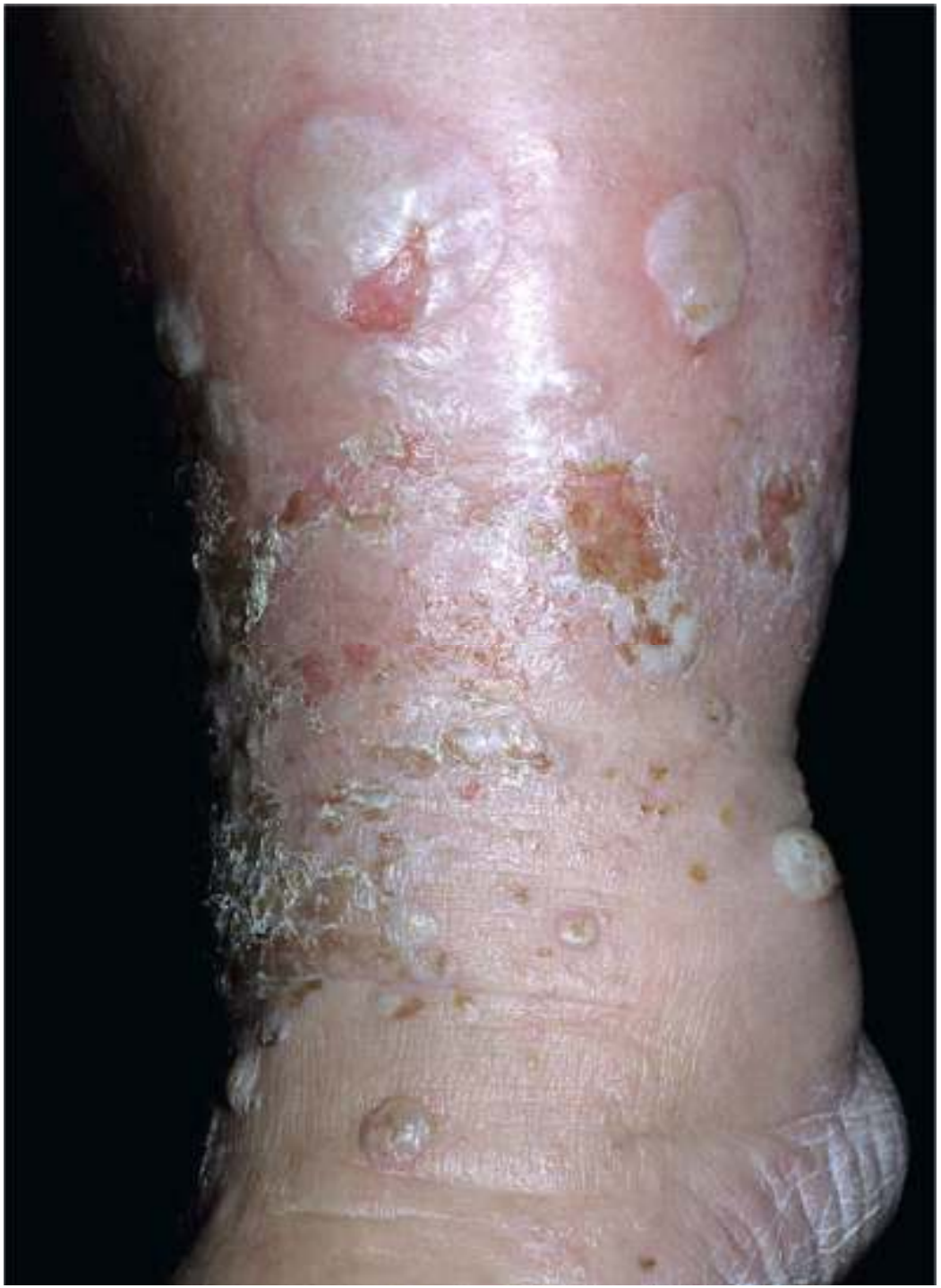
Dermatitis herpetiformis



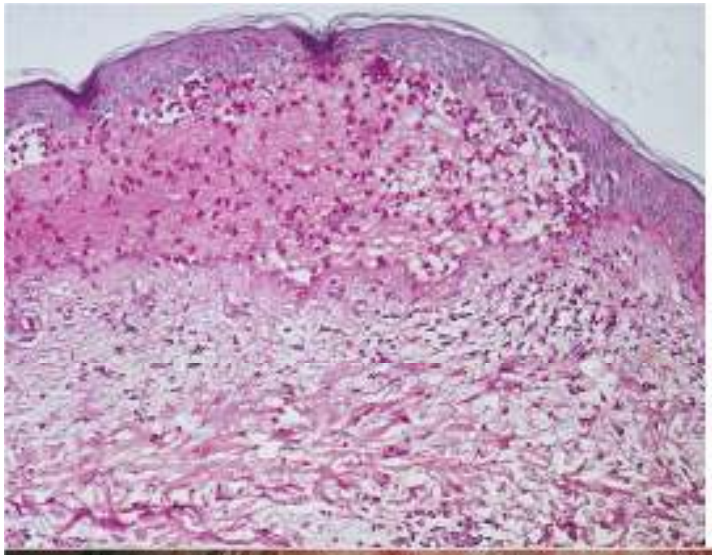




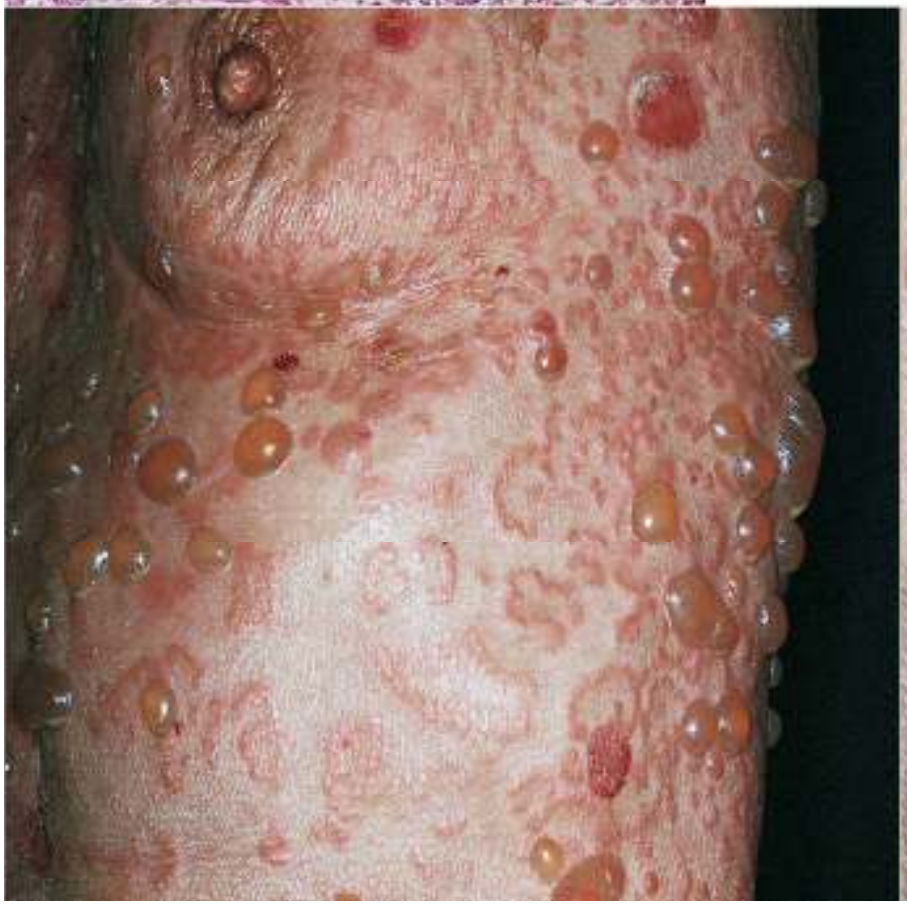


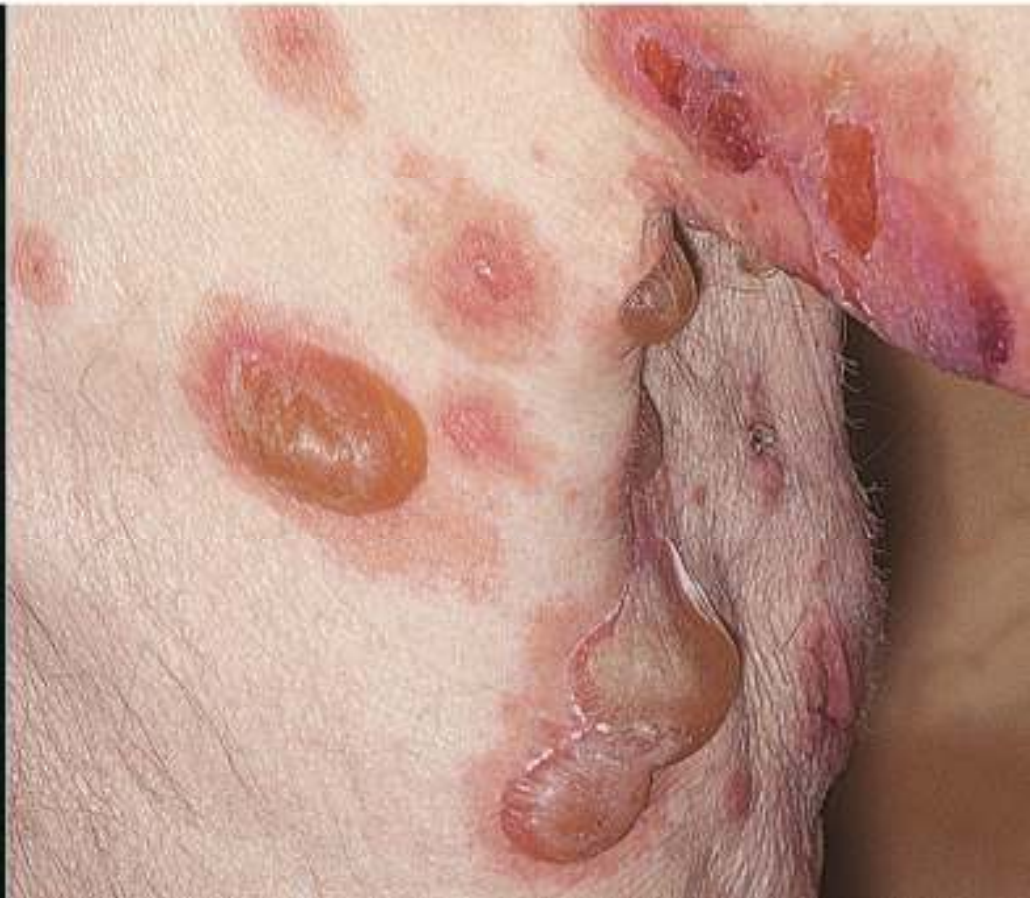


Bullosis diabeticorum

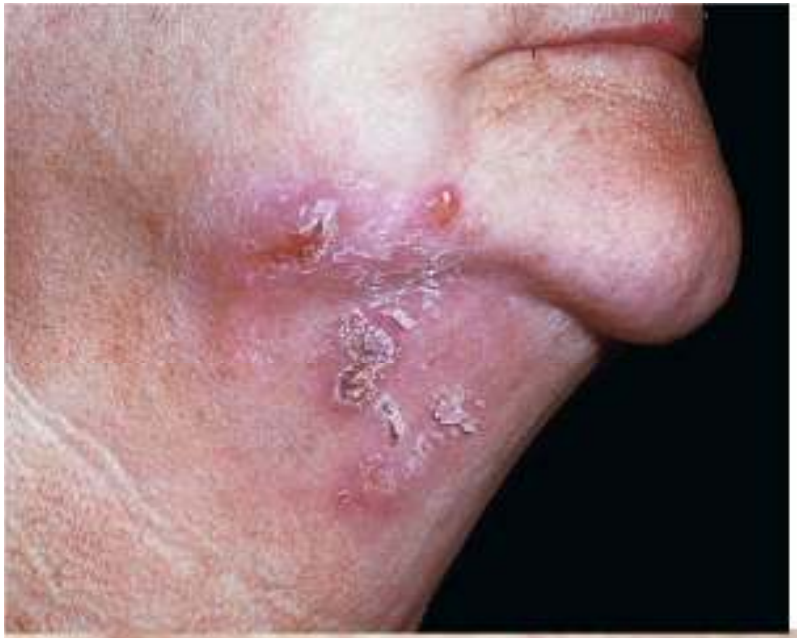


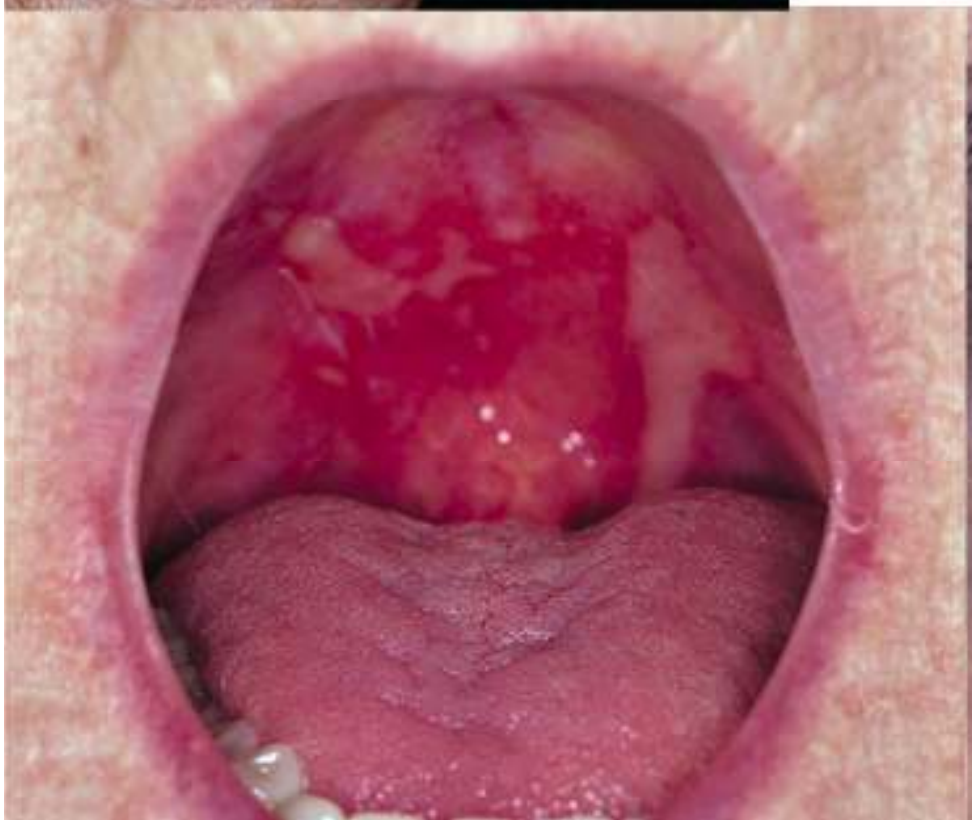
Bullous pemphigoid

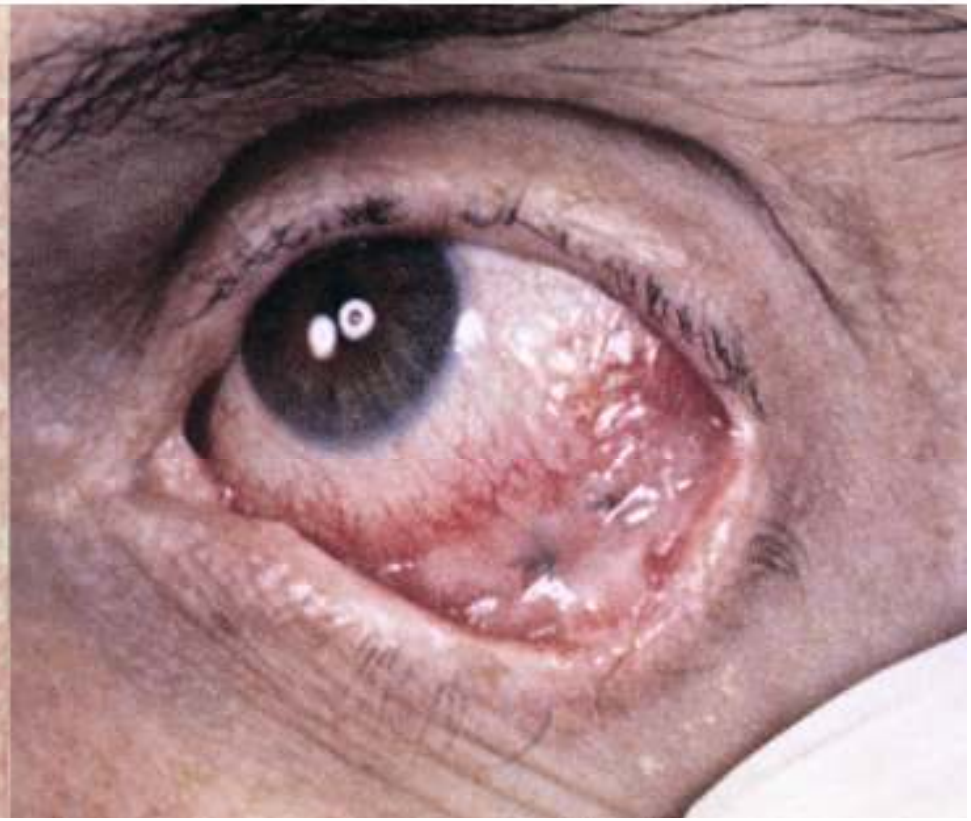




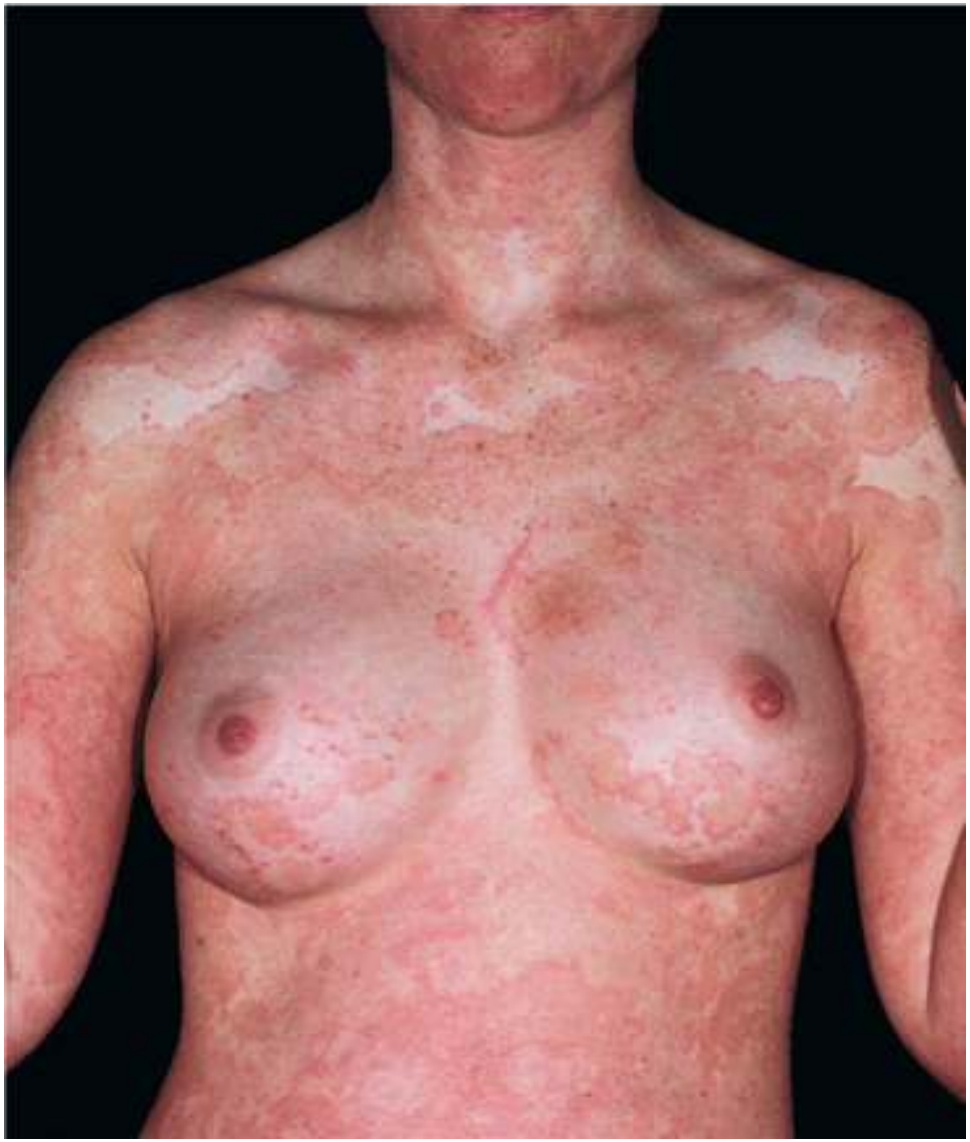
Cicatricial pemphigoid







Herpes (pemphigoid) gestationis
HLA-DR3 and HLA-DR4



Pemphigus treatment
Systemic corticosteroids

- This is the mainstay of therapy for most subtypes of pemphigus.
- Most flares can be controlled with between 1-3 mg/kg/day of prednisone divided into two doses.
- As blistering activity subsides, this daily dose can initially be tapered at a rate of 10 mg/week assessing closely for any recurrence of blisters.
- Once the patient reaches 60 mg/day, a single daily dose can be given.
- After patients have reached the 40 mg/day of prednisone point in their taper, further tapering of the average daily dose should be performed more cautiously, not more than an average of 5 mg/day decrease in dose per week as reflares occur frequently at this point.
- The dose of 20-30 mg/day (sustaining dose) has to be maintained for at least 5 years or for life.

Pemphigus treatment: Steroid sparing agents

- The use of a steroid sparing agent reduces the side effects encountered with systemic corticosteroids but care needs to be taken to monitor for systemic toxicity of the steroid sparing agents themselves including the increased risks of infection and malignancy.

- Probably the lease toxic steroid sparing regimen is the use of tetracycline 2g/day and nicotinamide 2g/day.

Pemphigus treatment: Steroid sparing agents

- Cyclophosphamide and azathioprine are the drugs most commonly used as a steroid sparing agents in pemphigus subtypes. Cyclophosphamide has significant potential systemic toxicity and patients must be carefully monitored during treatment which usually is a single daily dose of 1-2 mg/kg. Azathioprine in general has less systemic toxicity than cyclophosphamide but it works more slowly. It is given at a dose of 1-3 mg/kg/day.
- Other steroid sparing modalities for pemphigus which are sometimes effective include cyclosporin, chlorambucil and plasmapheresis. Intramuscular gold has also been reported to be of benefit to patients with pemphigus subtypes.

Pemphigus treatment: other therapies

- Plasmapharesis: in conjunction with glucocorticoids and immunosuppressive agents in poorly controlled patients, in the initial phases of treatment to reduce antibody titers;
- Gold therapy: for milder cases. After an initial test dose of 10 mg IM, 25-50 mg of gold sodium thiomalate is given IM at weekly intervals to a maximum cumulative dose of 1 g.

- Rituximab (anti-CD20 antibody).