
In the Name of GOD

Pemphigus

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Pemphigus

- Autoimmune blistering disease of skin and mucous membranes
- autoantibodies against desmoglein 3 and 1
- Three major types:
  - Vulgaris, Foliaceous and paraneoplastic
- IgA pemphigus (intraepidermal neutrophilic type and subcorneal pustular dermatosis type)

CLASSIFICATION OF PEMPHIGUS

- Pemphigus vulgaris
  - Pemphigus vegetans
- Pemphigus foliaceus
  - Pemphigus erythematosus: localized
  - Fogo selvagem: endemic
- Herpetiform pemphigus
- Drug-induced pemphigus*
- Paraneoplastic pemphigus
- IgA pemphigus

*Captopril, penicillamine

Table 29.1 Classification of pemphigus.

Epidemiology

- F=M
- 50-60 yerse
- PV> PF
- Fogo Selvagem: similar to pemphigus foliaceus, occurs in Brazil

Pathogenesis

- IgG against cell surface
- Maternal IgG crosses the placenta
- Complement activation and surface cross-linking is not essential in keratinocyte detachment
- Pemphigus vulgaris and foliaceus antigens are 130 kDa and 160 kDa
- Autoantibodies inhibit the adhesive function of desmogleins and lead to the loss of the cell–cell adhesion of keratinocytes, resulting in blister formation.

Humoral and Cellular Autoimmunity in Paraneoplastic Pemphigus

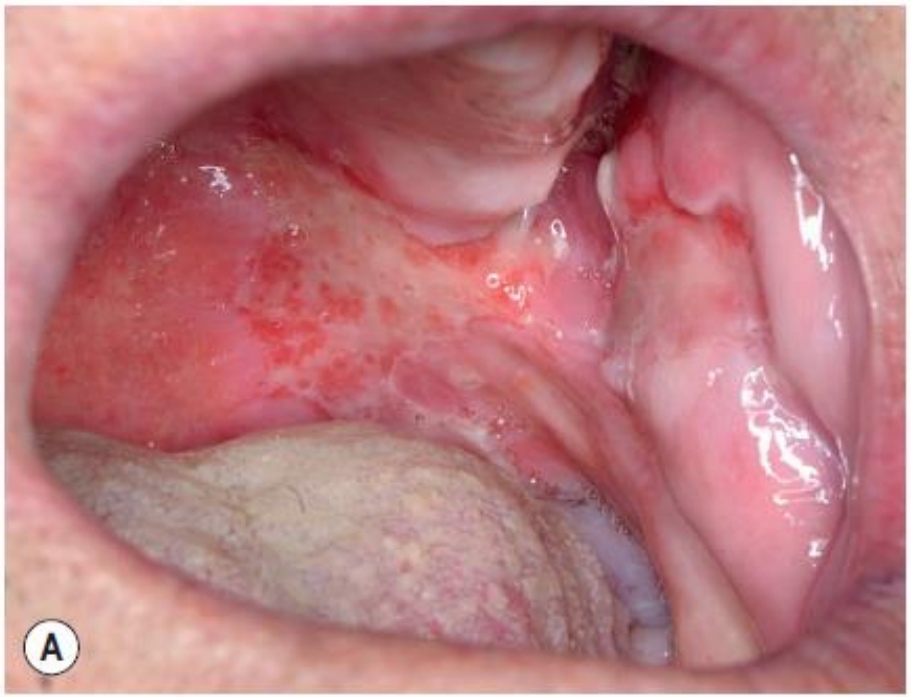
- IgG autoantibodies against multiple antigens (Dsg3 , Dsg1 and plakin)

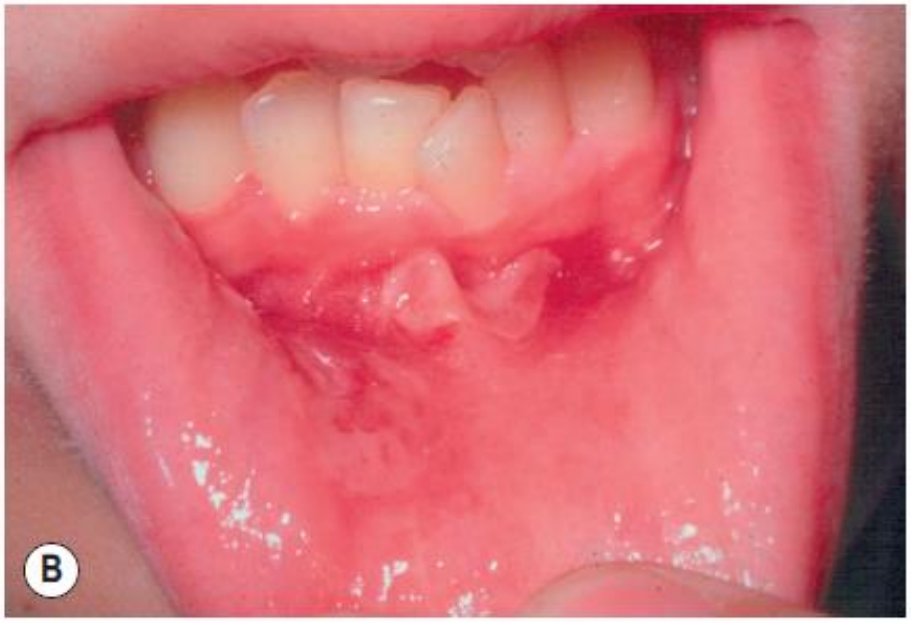
- cell-mediated cytotoxicity leads to more severe and refractory oral erosions and stomatitis and more polymorphic skin eruptions

Clinical Features

Pemphigus Vulgaris

- All patients have painful erosions of the oral mucosa (buccal and palatine), lip, throat, esophagus, conjunctivae, nasal mucosa, vagina, labia, penis and anus
- Flaccid, blisters on the normal-appearing and erythematous skin
- Leave hyperpigmented patch with no scar
- Nikolsky sign, Asboe–Hansen sign
- Death due to loss of body fluids or secondary bacterial infections





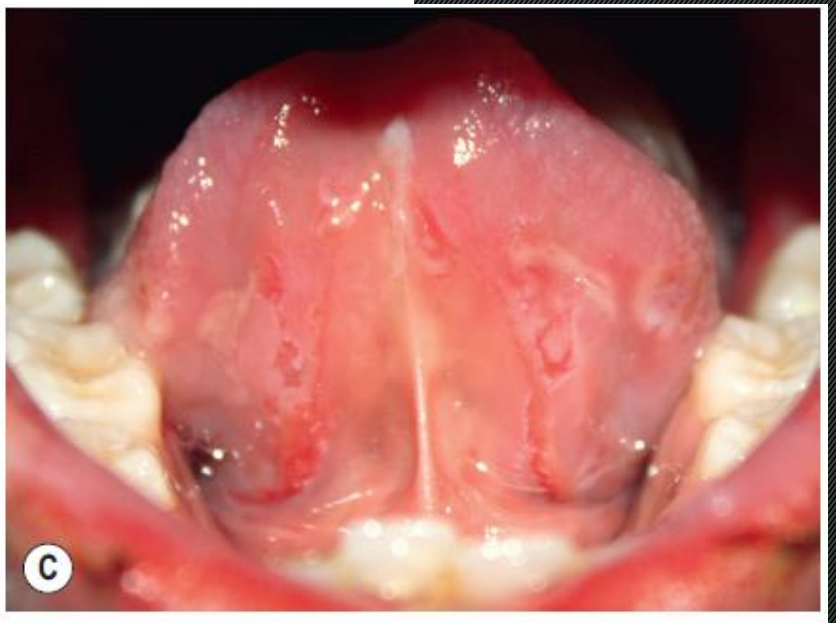
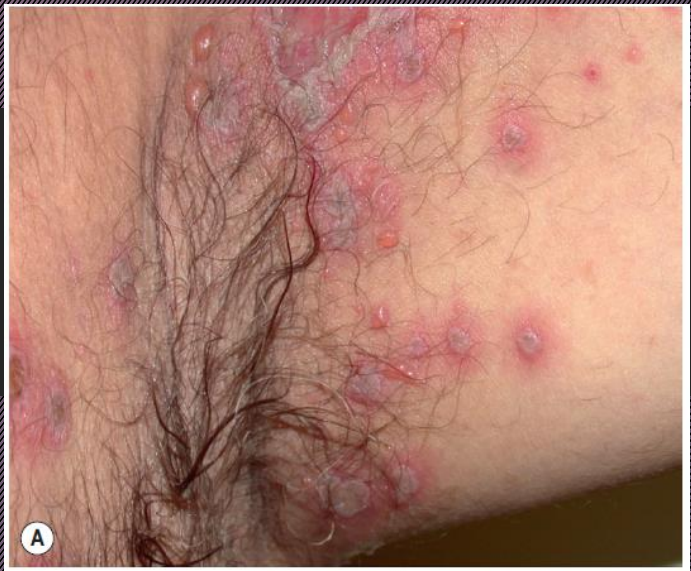
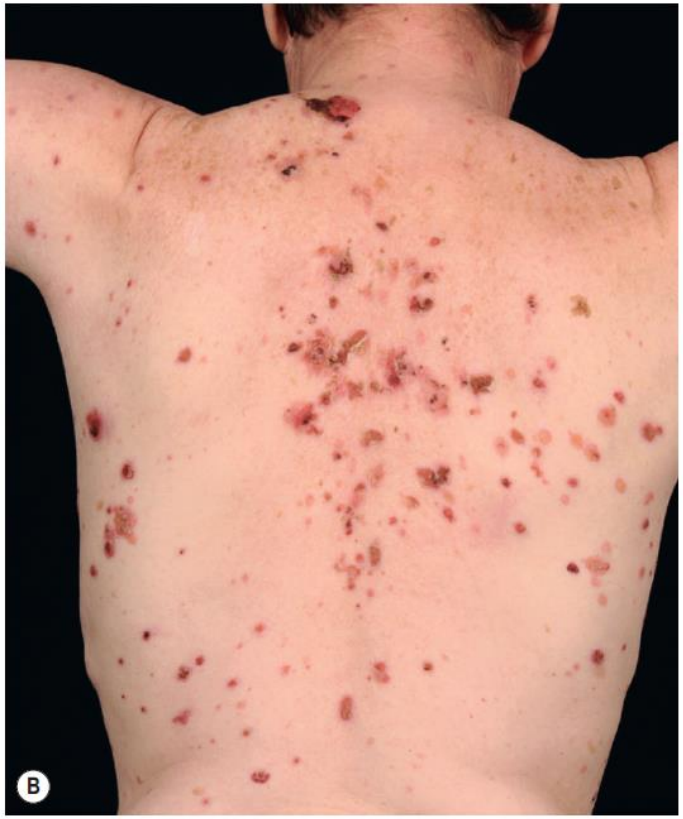


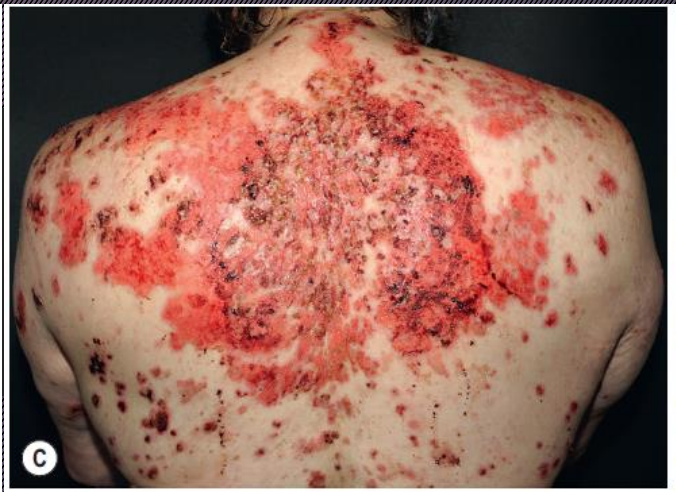
Fig. 29.5 Pemphigus vulgaris – oral involvement. Essentially all patients develop painful oral mucosal erosions. The most common sites are the buccal (**A**) and palatine mucosae, but lesions can also develop on the gingivae (**B**) and tongue (**C**). *A, Courtesy, Lorenzo Cerroni, MD; B,C, Courtesy, Jeffrey P Callen, MD.*

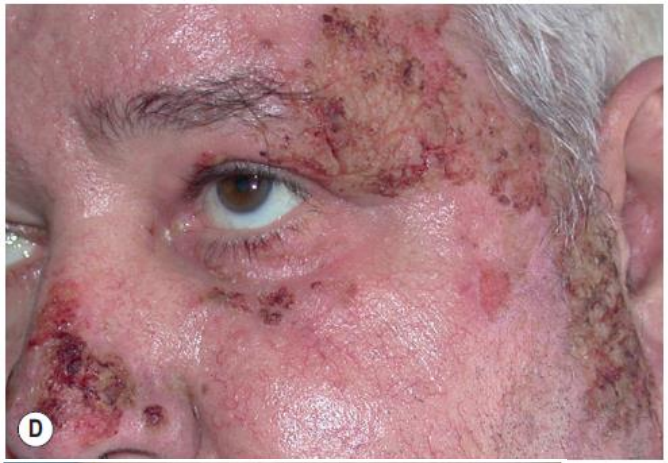
UNUSUAL CLINICAL PRESENTATIONS OF PEMPHIGUS VULGARIS
Isolated crusted plaque on face or scalp
Paronychia and/or onychomadesis
Foot ulcers
Dyshidrotic eczema or pompholyx
Macroglossia

Table 29.3 Unusual clinical presentations of pemphigus vulgaris.









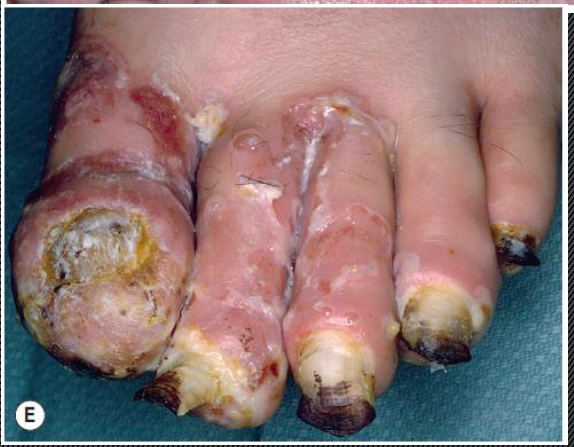


Fig. 29.6 Pemphigus vulgaris – cutaneous involvement. **A** Flaccid blisters and an erosion due to rupture of a bulla. **B,C** Multiple erosions and hemorrhagic crusts of the back that can become extensive. Secondary bacterial infections are a potential complication. **D** A vegetative response can occasionally be seen in chronic recalcitrant lesions; the patient has a Cushingoid appearance due to use of chronic systemic corticosteroids. **E** The dyshidrosiform variant is uncommon. *A,D, Courtesy, Luis Requena, MD; B,C, Courtesy, Lorenzo Cerroni, MD; E, Courtesy, Louis A Fragola, Jr, MD.*

Clinical Features

Pemphigus Vegetans

- Reactive pattern of the skin to the autoimmune insult of pemphigus vulgaris

- Fungoid vegetations or papillomatous proliferations, especially in intertriginous areas and scalp or face

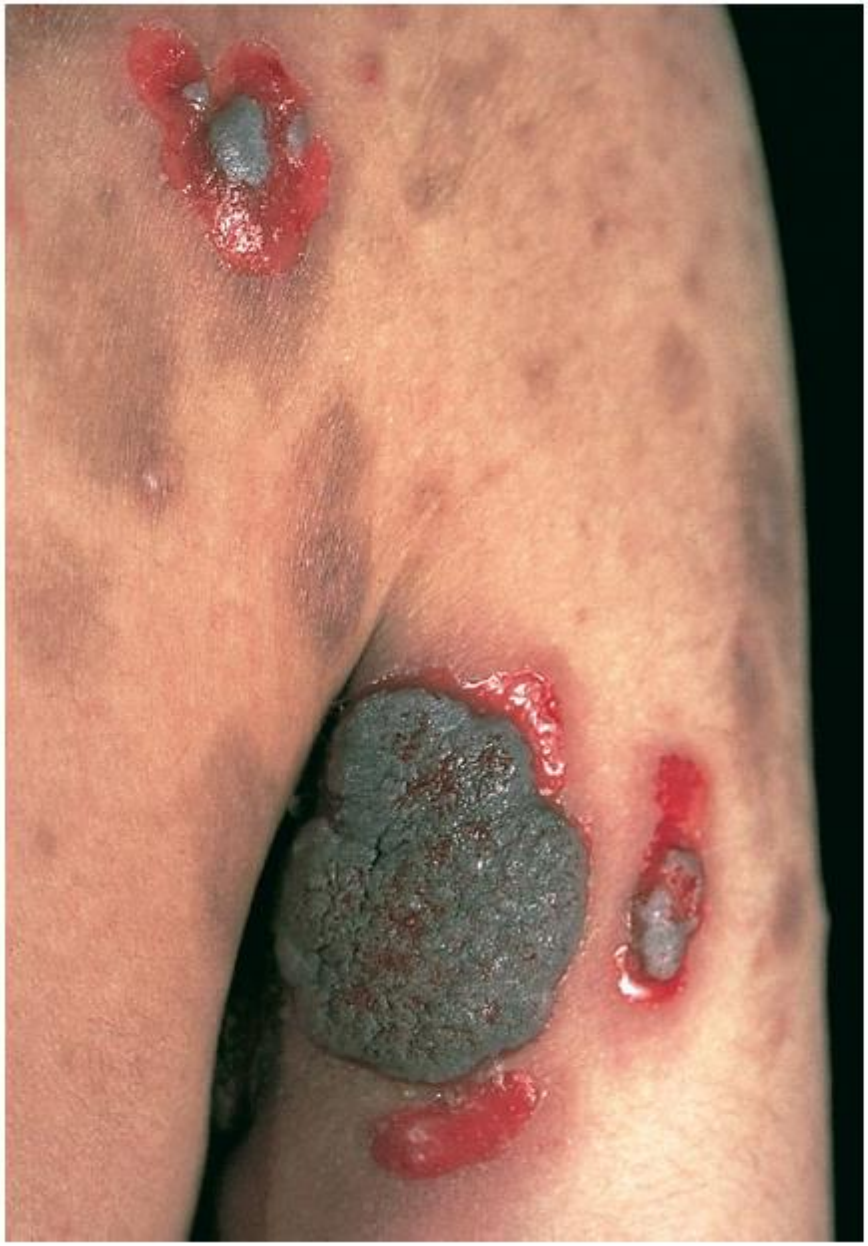


Fig. 29.7 Pemphigus vegetans. Large, thick, vegetating, papillomatous plaques arising in conjunction with erosions. Healed lesions have residual postinflammatory hyperpigmentation.

Clinical Features

Pemphigus Foliaceus

- Scaly, crusted cutaneous erosions, often on an erythematous base
- No clinically apparent mucosal involvement
- Crusted lesions with seborrheic distribution
- May stay localized or rapidly progress to erythroderma
- Nikolsky sign Positive
- Mucosal involvement is extremely rare

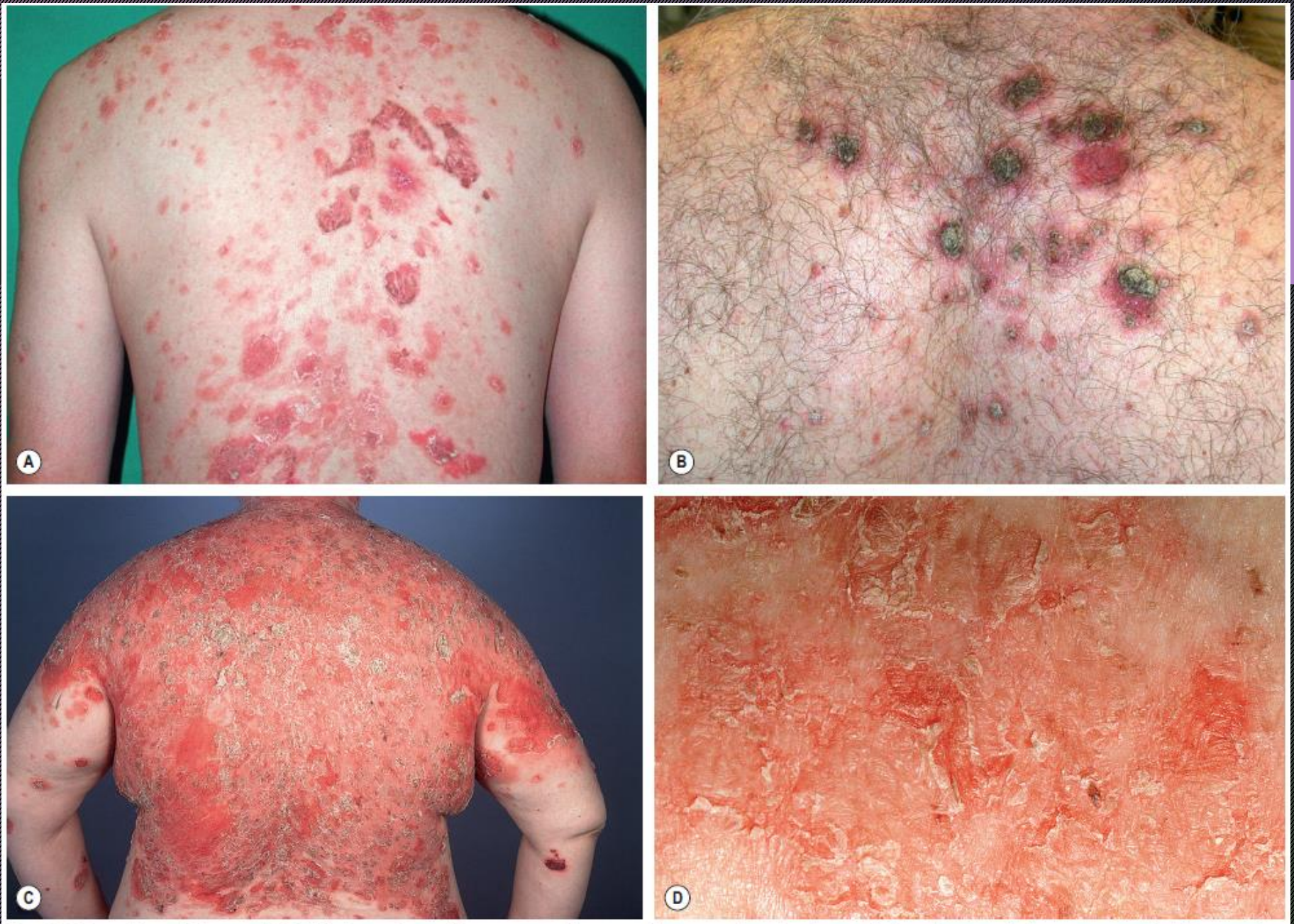


Fig. 29.8 Pemphigus foliaceus. **A**,**B** Multiple erosions arising on an erythematous base as well as the characteristic scale-crust; the latter can vary in thickness. A common site of involvement is the trunk. **C** As the disease progresses, the lesions become confluent, but because the vesicles are fragile and rupture easily, only erosions with scale-crust are observed. **D** The scales have been likened to cornflakes.

Clinical Features

Pemphigus Erythematosus

- A localized variant of pemphigus foliaceus

- Originally describe patients with both lupus erythematosus (LE) and pemphigus (IgG and C3 deposition on cell surfaces of keratinocytes and BMZ) with circulating antinuclear antibodies.

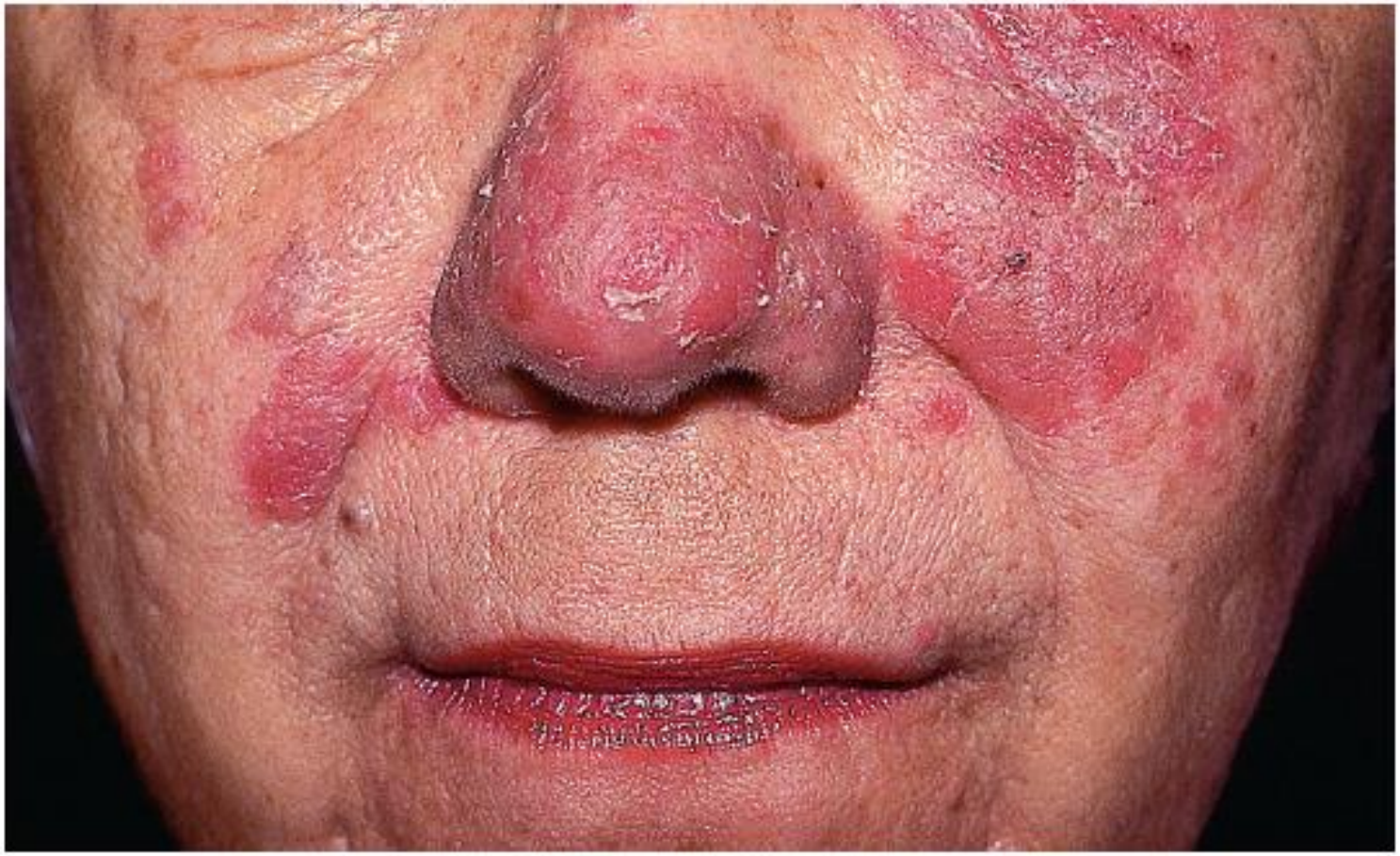


Fig. 29.9 Pemphigus erythematosus. Erythematous plaques with scale-crust and erosions on the nose and malar area of the face. *Courtesy, Ronald P Rapini, MD.*

Clinical Features

Herpetiform Pemphigus

- Most have a clinical variant of pemphigus foliaceus and the remainder pemphigus vulgaris
- Erythematous urticarial plaques and tense vesicles in herpetiform arrangement
- Eosinophilic spongiosis and subcorneal pustules with minimal and no acantholysis
- IgG against cell surfaces (Dsg1 and Dsg3)

Clinical Features

Drug-Induced Pemphigus

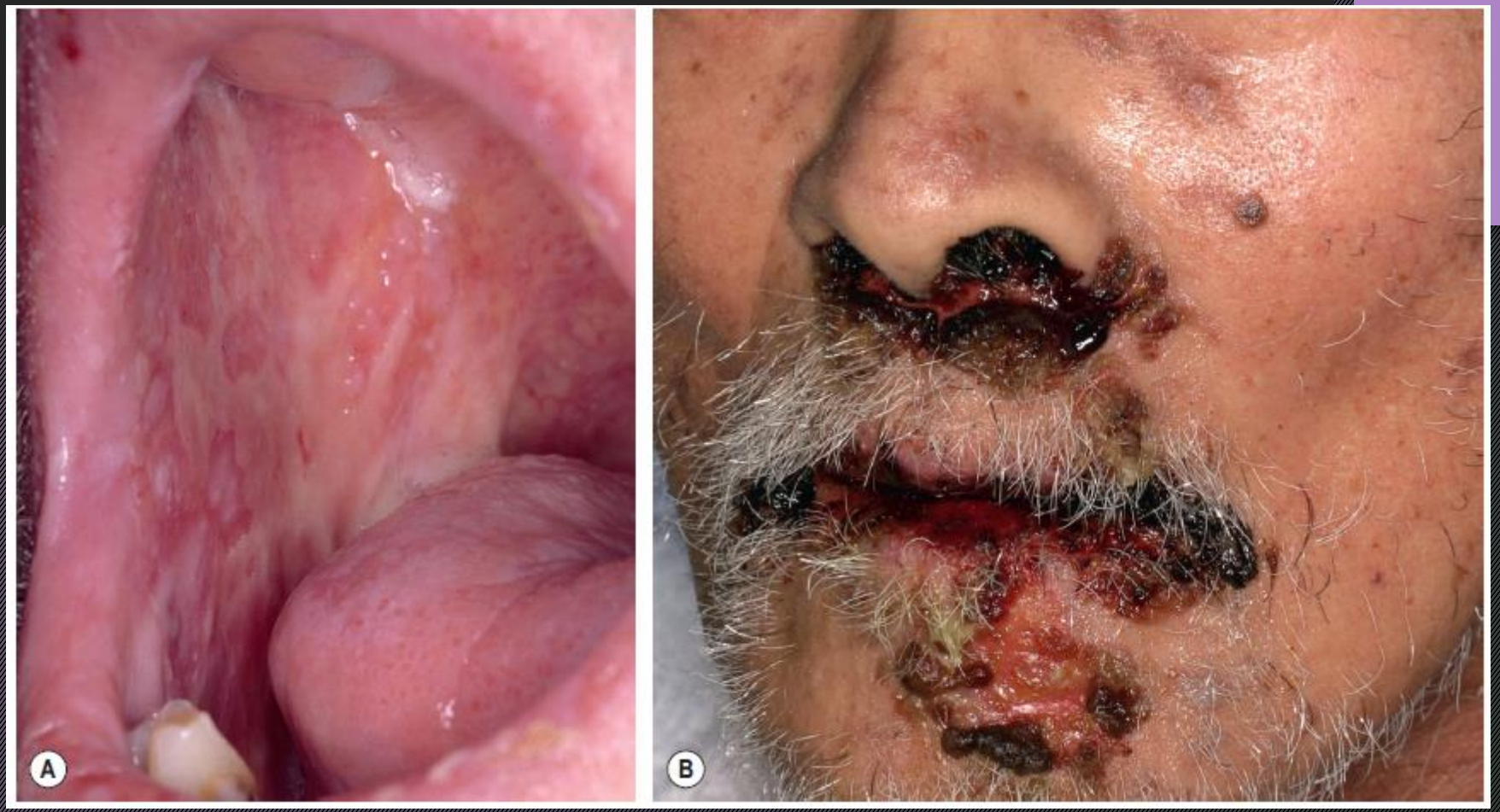
- Penicillamine (pemphigus foliaceus /pemphigus vulgaris =4:1) and captopril: Contain Sulfhydryl groups that interact with sulfhydryl groups in Dsg1 and Dsg3, modify the antigenicity of the desmogleins, leads to autoantibody production

- Most go into remission after the offending drug is discontinued

Clinical Features

Paraneoplastic Pemphigus

- Underlying neoplasms (malignant and benign).
- Non-Hodgkin lymphoma and chronic lymphocytic leukemia, 2/3 in adults and castleman disease in children and adolescents, malignant and benign thymomas, sarcomas and Waldenström macroglobulinemia
- The most constant clinical feature → intractable stomatitis, presenting sign, resistant to therapy, as erosions and ulcers affect all surfaces of the oropharynx and characteristically extend onto the vermilion lip , severe pseudomembranous conjunctivitis, Nasopharyngeal, esophageal, vaginal, labial, penile and perianal lesions
- polymorphic Cutaneous findings:
  - Erythematous macules, blisters (flaccid or tense) erosions erythema multiforme-like lesions (differentiate from pemphigus vulgaris), and lichenoid eruptions

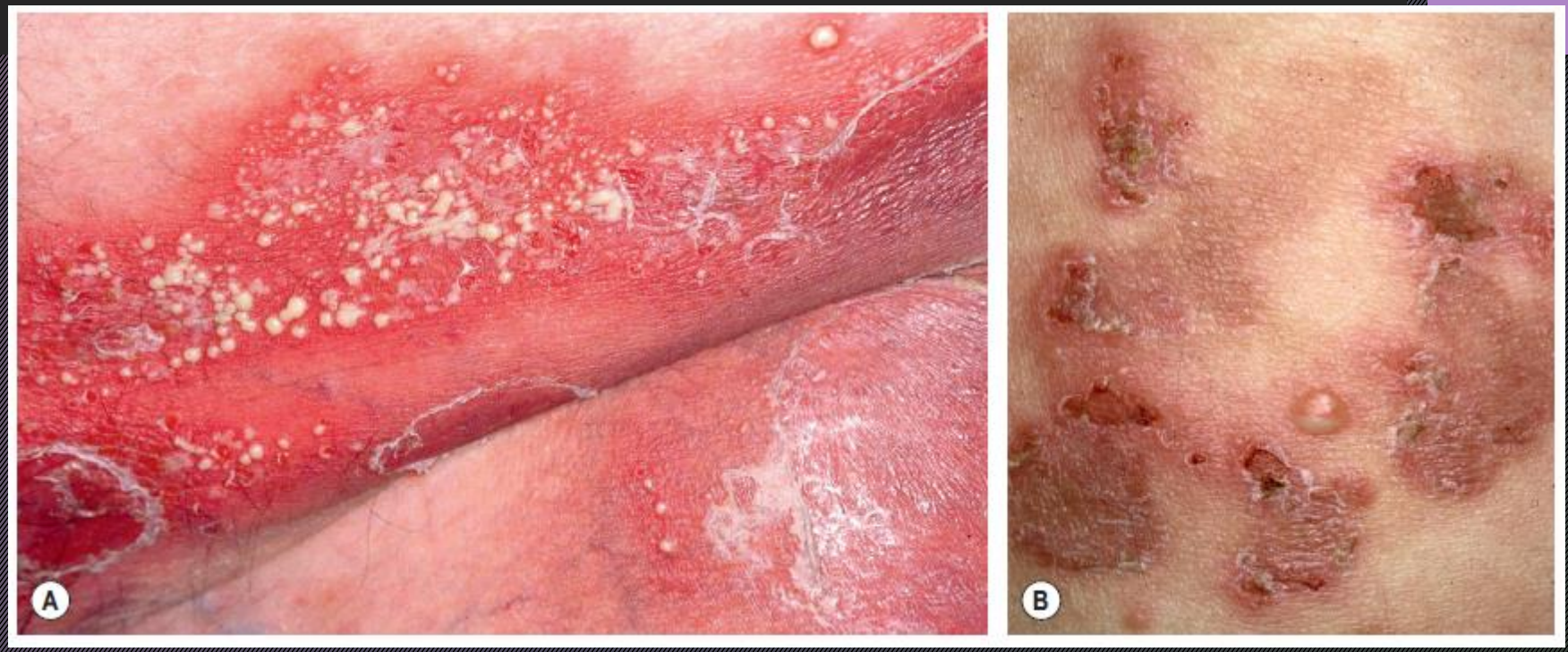


- **Fig. 29.10** Paraneoplastic pemphigus. **A** The characteristic clinical feature is severe intractable stomatitis with multiple erosions; there may be a resemblance to erosive oral lichen planus. **B** The erosions, along with hemorrhagic crusts, can extend onto the vermilion lip and involve the nasal mucosa. *A, Courtesy, Luis Requena, MD.*

Clinical Features

IgA Pemphigus

- Vesiculopustular eruption
- Middle-aged or elderly
- Subcorneal pustular dermatosis type and the intraepidermal neutrophilic type
- Flaccid vesicles or pustules on either erythematous or normal skin circinate pattern, sunflower-like configuration of pustules characteristic for intraepidermal neutrophilic type
- Axilla and groin, extremities, rarely mucous membrane and pruritus



- **Fig. 29.11** IgA pemphigus – subcorneal pustular dermatosis (SPD) type. **A** Numerous superficial pustules arising within areas of erythema; these pustules rupture easily. The desquamation has a figurate configuration and overall there is a resemblance to ustular psoriasis. **B** Pustules tend to coalesce to form an annular or figurate pattern with crusts present centrally. Note the accumulation of the pustular component in the dependent portion of the vesiculopustule. *A, Courtesy, Luis Requena, MD.*

Pathology

- Pemphigus Vulgaris:
  - Suprabasilar acantholysis and blister without keratinocytes necrosis
- Pemphigus Vegetans:
  - Suprabasilar acantholysis with papillomatosis and acanthosis
- Pemphigus Foliaceus:
  - Acantholysis within or adjacent to the granular layer
- Paraneoplastic Pemphigus:
  - Polymorphism (combination of pemphigus vulgaris, erythema multiforme and lichen planus), suprabasilar acantholysis and keratinocyte necrosis
- IgA Pemphigus:
  - intraepidermal pustule or vesicle with out acantholysis

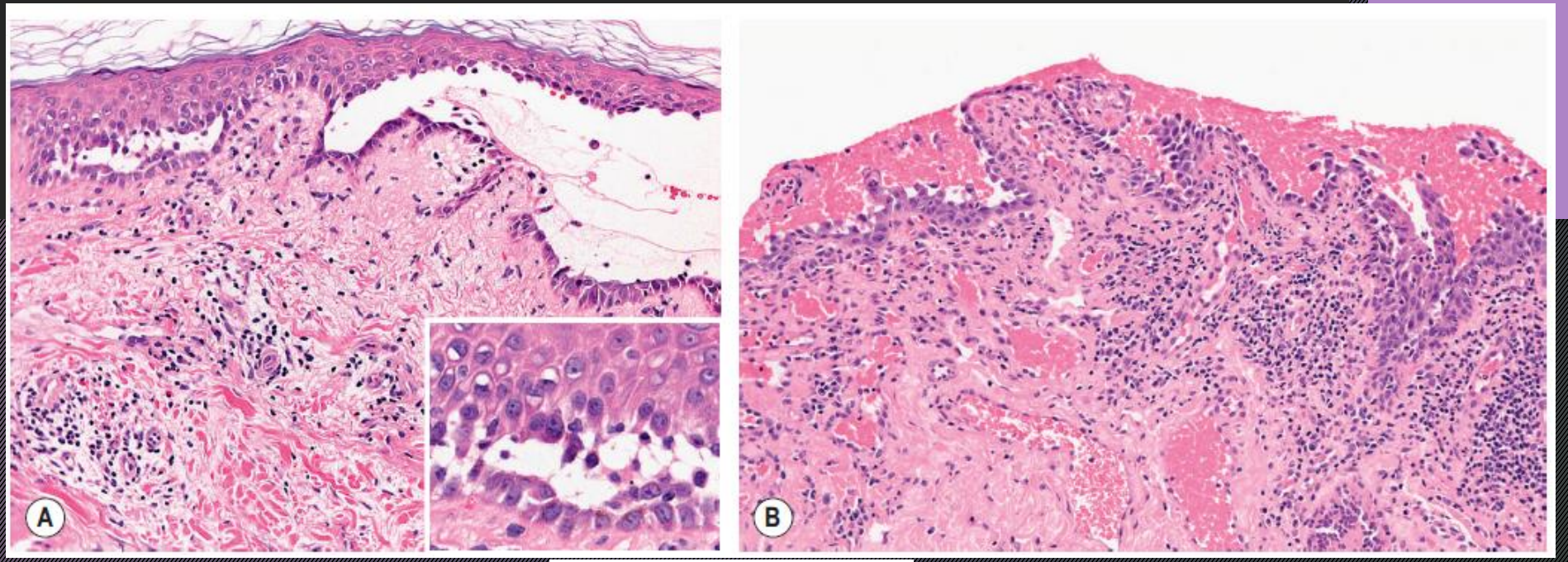


Fig. 29.13 Pemphigus vulgaris – histologic features. A Blisters in the skin show suprabasilar acantholysis with a few acantholytic cells in the blister cavity (inset). **B** Because blisters in the mouth rarely remain intact, the blister roof is often not seen in oral biopsy specimens. Nonetheless, the diagnosis can be made by the location of the split within the epithelium, the presence of acantholytic cells, and the "tombstones" appearance of the basal cells. *Courtesy, Lorenzo Cerroni, MD.*

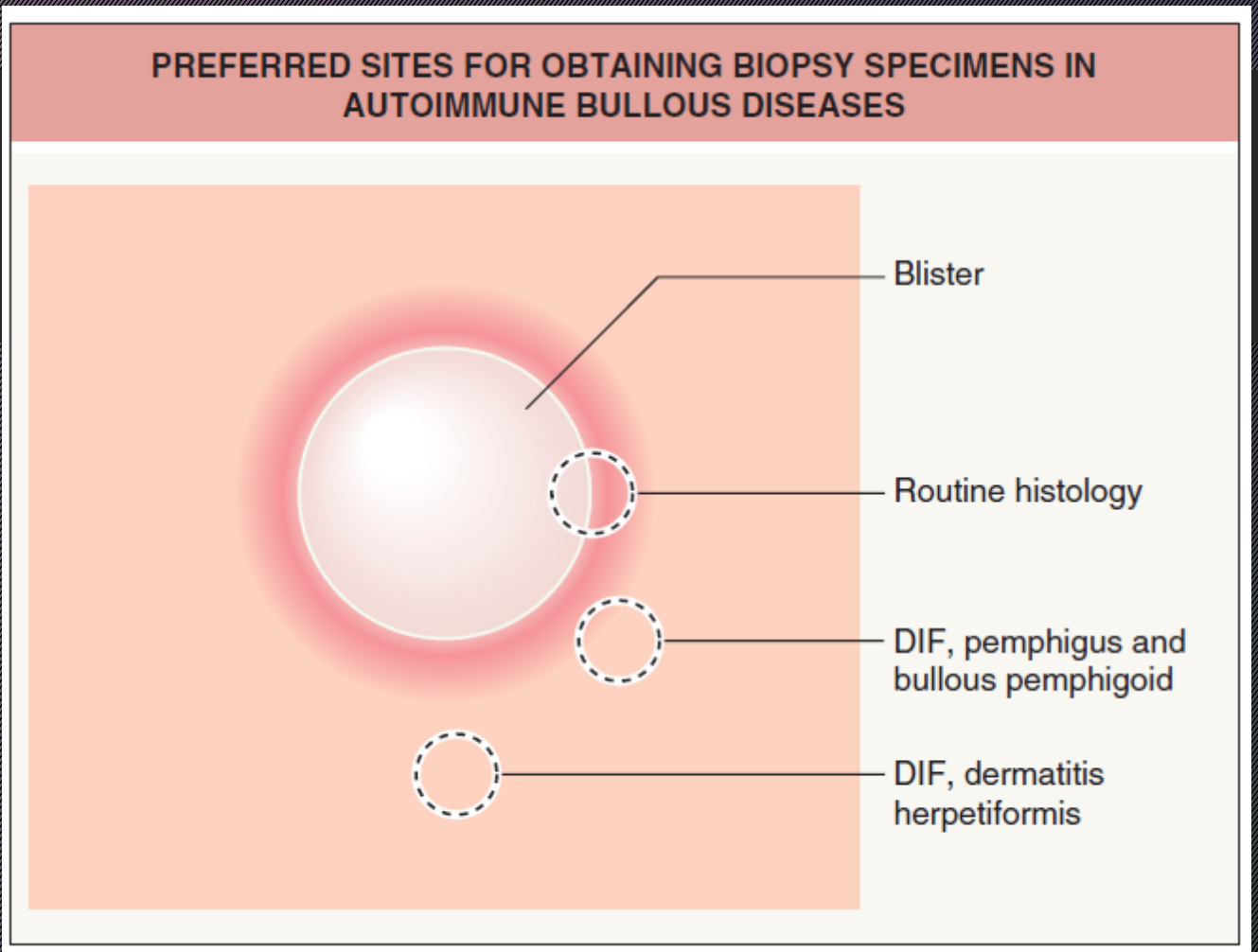


Fig. 29.12 Preferred sites for obtaining biopsy specimens in autoimmune bullous diseases. If the lesion is small enough, the entire vesicle can be removed for routine histology. If the lesions are not small, the edge of a fresh vesicle or bulla plus the inflammatory rim is recommended. For direct immunofluorescence (DIF) for various forms of pemphigus and bullous pemphigoid, perilesional skin is preferred, whereas nearby normal skin is recommended in dermatitis herpetiformis.

Differential Diagnosis

- Spongiotic dermatitis, burns, TEN, systemic LE, lichen planus, aphthous stomatitis, erythema multiforme, Stevens–Johnson syndrome, cicatricial pemphigoid, subcorneal pustular dermatosis, seborrheic dermatitis, Hailey–Hailey disease.

DISORDERS WITH HEMORRHAGIC CRUSTS OF THE VERMILION LIPS

Herpes simplex
Herpes zoster
Erythema multiforme major
Stevens–Johnson syndrome/TEN spectrum
Pemphigus vulgaris
Paraneoplastic pemphigus
Contact cheilitis

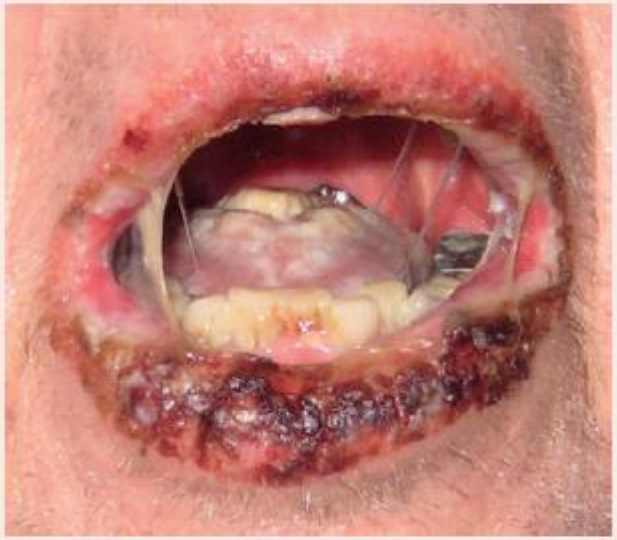


Table 29.8 Disorders with hemorrhagic crusts of the vermilion lips.
Photograph, courtesy, Jeffrey P Callen, MD.

Treatment

- Fatal within 2–5 years of the onset
- Pemphigus foliaceus has a better prognosis
- Systemic corticosteroids, high-dose IVIg and rituximab
- Immunosuppressive agents:
  - Azathioprine, mycophenolate, mofetil and cyclophosphamide

THERAPEUTIC LADDER FOR PEMPHIGUS VULGARIS	
Standard treatment	
Oral prednisone	1 mg/kg/day as an initial dose (usually 60 mg/day) (1)
Aggressive treatment	
Immunosuppressive agents in combination with oral prednisone:	
Azathioprine	2–4 mg/kg/day (usually 100 to 300 mg/day) (1)
Mycophenolate mofetil	2–3 g/day (2)
Cyclophosphamide	1–3 mg/kg/day (usually 50 to 200 mg/day) (2)
Cyclosporine	3–5 mg/kg/day (2)
Pulse methylprednisolone	1 g/day over a period of 2–3 hours for 3–5 consecutive days (2)
Methotrexate	7.5–20 mg/week (3)
Pulse cyclophosphamide	500–1000 mg/m^2 every 4 weeks (3)
Plasmapheresis	1–2 times per week, at the onset (2)
High-dose IVIg	400 mg/kg/day for 5 consecutive days (1); may need to be repeated monthly
Rituximab	375 mg/m^2 once weekly for 4 weeks (2) or 1 g initially then at two weeks; either regimen may need to be repeated every 3–6 months (1)
Extracorporeal photopheresis	2 days per month (3)
Topical treatment	
Topical corticosteroids (1), especially Class I to localized persistent sites Topical antibiotics (2) Topical immunomodulators (e.g. cyclosporine, tacrolimus) (3)	
Intralesional therapy	
Corticosteroids (3) Rituximab (5 mg/cm^2) (3)	

Table 29.9 Therapeutic ladder for pemphigus vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.


The END