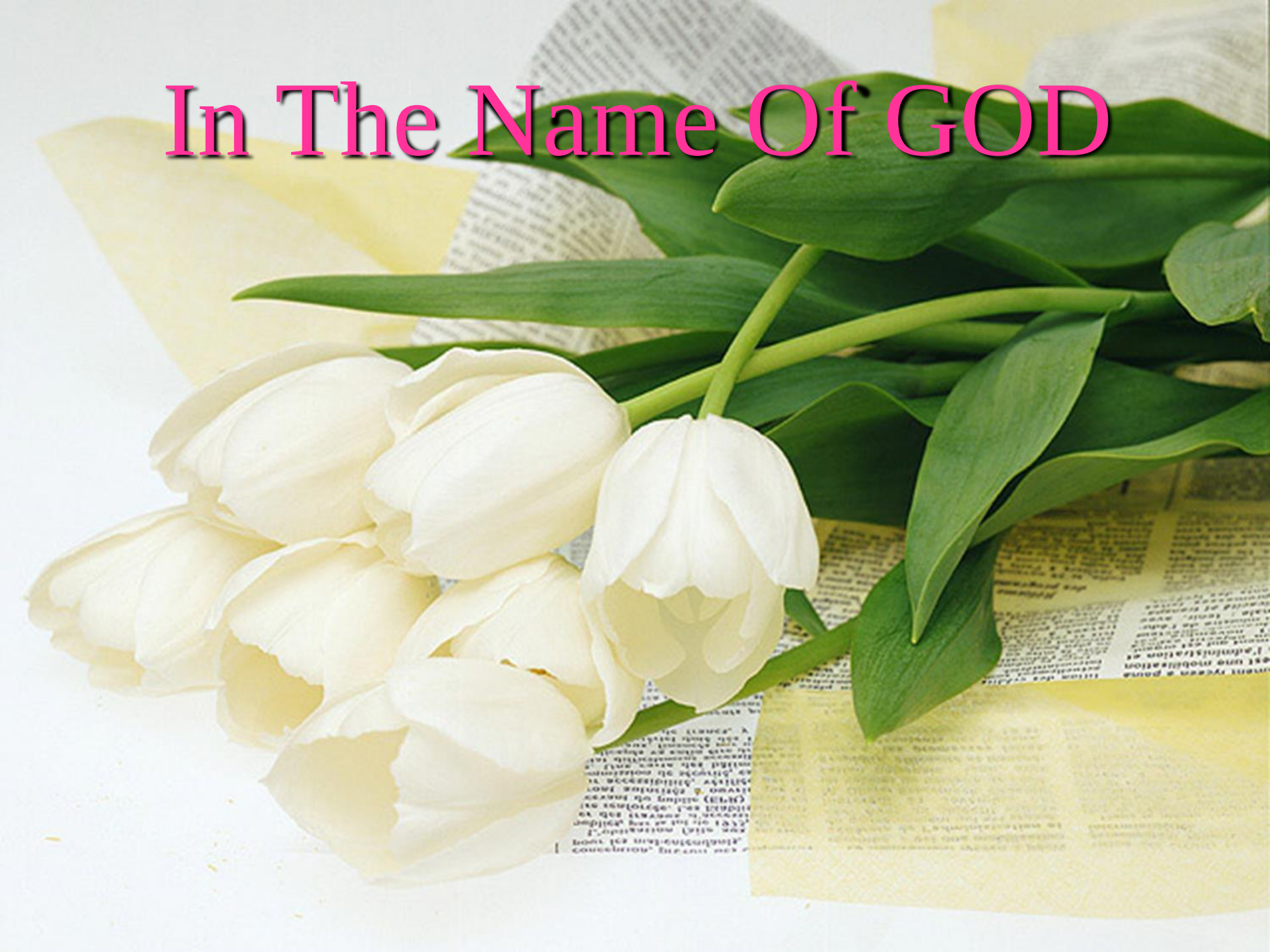
In The Name Of GOD

Bullous Pemphigoid

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Introduction

- Most common Autoimmune subepidermal blistering dis.
- Typically: older adult with significant morbidity
- Clinical presentation can be polymorphic (especially in early stage)

History

- During 18 century → all say pemphigus
- In 1953: lever recognized BP
- 10 years later: Antibodies against BMZ.

Epidemiology

- Typically older adult
- Onset: after 60 years
- 6-13 new case/million in a year
- Over 90 years → 300 fold higher
- M> F
- Children: rare

Pathogenesis

- Immune mediated dis. (Auto Ab produting)
- Normal and cellular response directed againt Two Ag
- BPAG 180 (BPAG 2 or XVII collagen)
- BPAG 230 (BPAG 1)
- AG 180: Transmembrane protein
- AG 230: Cytoplasmic Protein
- Both are component of hemidesmosoms

MAJOR AUTOANTIGENS OF SUBEPIDERMAL AUTOIMMUNE-MEDIATED BLISTERING DISEASES			
Disease	**Target antigen(s)**	**Mol. wt. (kDa)**	**Morphologic structures**
Bullous pemphigoid (BP)	BP180/BPAG2/collagen XVII BP230/BPAG1e	180 230	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque
Gestational pemphigoid	BP180/BPAG2/collagen XVII BP230/BPAG1e	180 230	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque
Mucous membrane (cicatricial) pemphigoid	BP180/BPAG2/collagen XVII BP230/BPAG1e† Laminin 332 (laminin 5; $\alpha_3\beta_3\gamma_2$; epiligrin) Laminin 311 (laminin 6; $\alpha_3\beta_1\gamma_1$)‡ Integrin β_4 subunit§	180 230 165, 140, 105 165, 220, 200 200	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque Anchoring filaments Anchoring filaments/extracellular matrix Hemidesmosomal plaque/anchoring filaments
Linear IgA bullous dermatosis (LABD)	LAD antigen¶ BP180/BPAG2/collagen XVII BP230/BPAG1e† Type VII collagen†	97/120 180 230 290/145	Anchoring filaments Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque Anchoring fibrils
Epidermolysis bullosa acquisita	Type VII collagen†	290/145	Anchoring fibrils
Anti-laminin γ1 pemphigoid (previously known as anti-p200 pemphigoid)	Laminin gamma-1 chain	200	Extracellular matrix
Bullous systemic lupus erythematosus	Type VII collagen†	290/145	Anchoring fibrils

†Detectable in a subset of patients.
‡Binding to laminin 311 depends on the presence of cross-reactive autoantibodies directed against the α-chain of laminin 332 (laminin 5).
§Reactivity with the cytoplasmic domain of the β_4 subunit of the $\alpha_6\beta_4$ integrin described in a subset of patients with *ocular* cicatricial pemphigoid.
¶It constitutes the most characteristic serologic marker for LABD. The 120 kDa LAD antigen corresponds to the cleaved, shed extracellular domain of BP180/BPAG2. The 97 kDa protein results from its further proteolytic degradation (see Fig. 31.9).

Table 30.1 Major autoantigens of subepidermal autoimmune-mediated blistering diseases. Not an exhaustive list. In the course of these diseases, it is possible to detect autoantibodies directed against additional antigens, the significance of which remains to be established. In certain cases, a so-called "intermolecular epitope spreading" phenomenon is thought to occur.

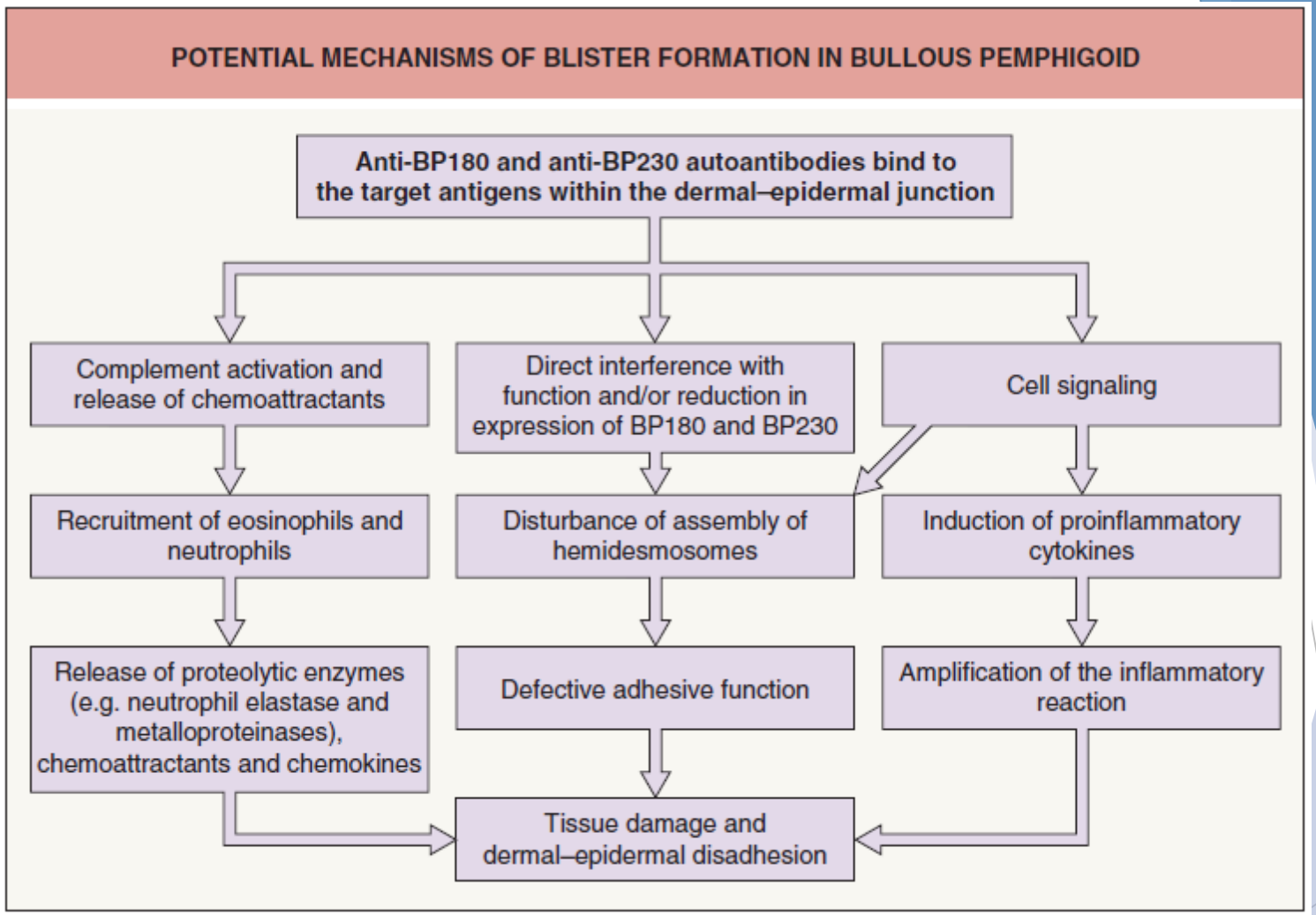


Fig. 30.1 Potential mechanisms of blister formation in bullous pemphigoid. IgG autoantibodies are classically involved in the pathogenesis, but more recently IgE autoantibodies have also been described.

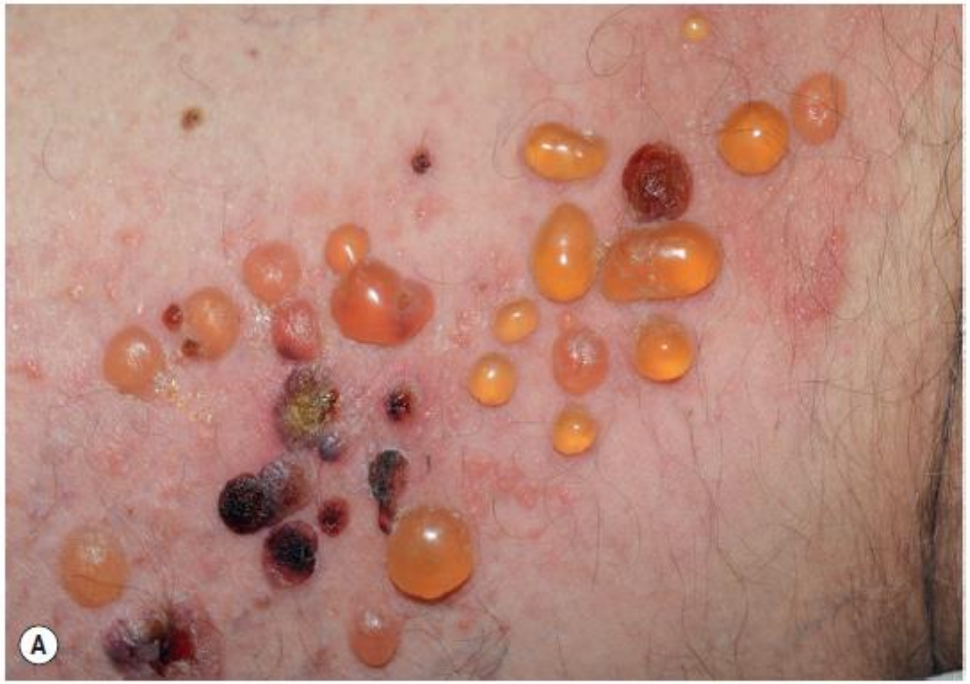
Clinical Feature

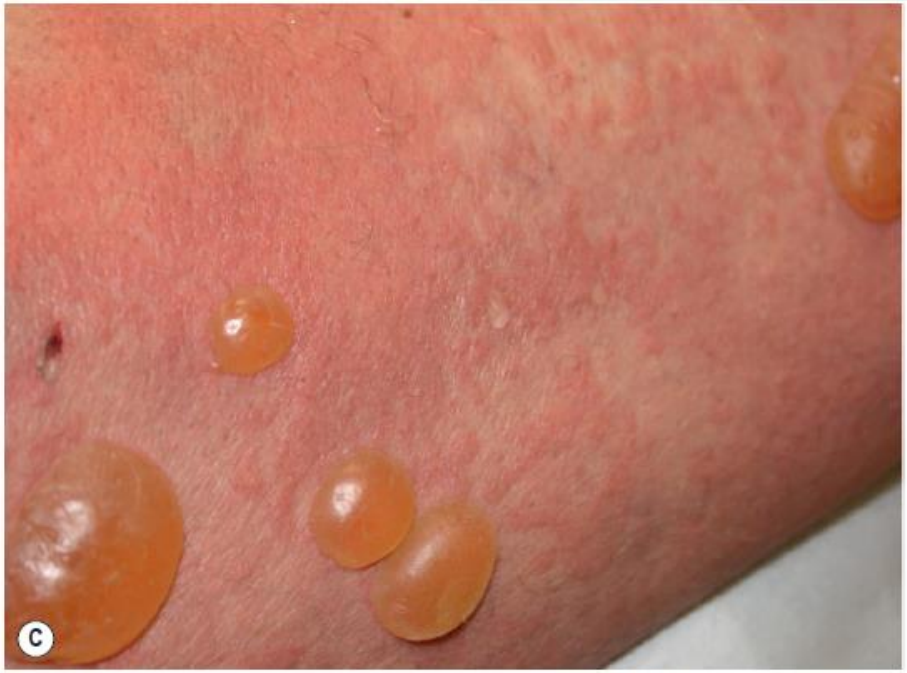
Non- Bullous Pemphigoid

- Non specific
- Intractable pruritus alone
- Excoriated- Eczematous, Papular, Urticarial lesions for several weeks or months
- Occasionally this stage remain as the only signs of disease
- 20% patients have neither blister nor erosion at the time of diagnosis

Bullous Phase

- Vesicle+ Bullae on normal or erythematous skin
- Together with urticarial and infiltrative papule and plaques
- Blister: tense- Up to 1- 4 cm- contain clear fluid or hemorrhagic
- Symmetric distribution
- Often flexural aspect+ low trunk
- Oral cavity → 10-30%
- 50% → Blood eosinophilia





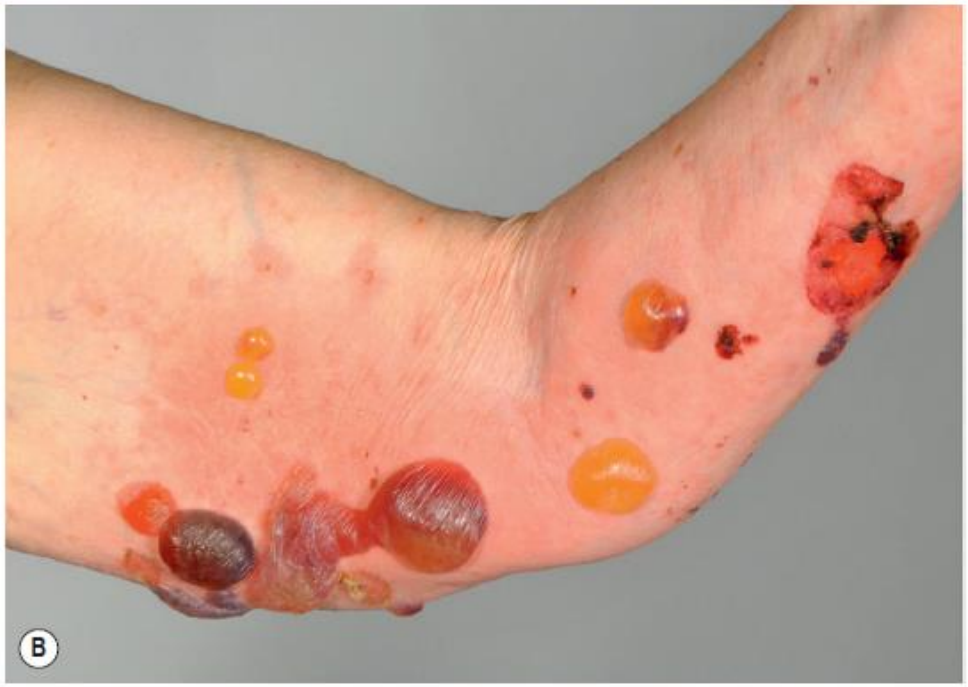


Fig. 30.2 Bullous pemphigoid – classic presentation. A–C Tense vesicles and bullae vary in size from a few mm to several cm in diameter and can arise within normal-appearing skin, areas of erythema, or urticarial plaques. The blister fluid may be serous or hemorrhagic. The flexor aspect of the extremities is a common site of involvement. As the bullae age, they become flaccid and rupture, leaving erosions and serous or hemorrhagic crusts. Biopsies of vesiculobullae for routine histology should be obtained from fresh tense blisters. *A, Courtesy, Kalman Watsky, MD.*

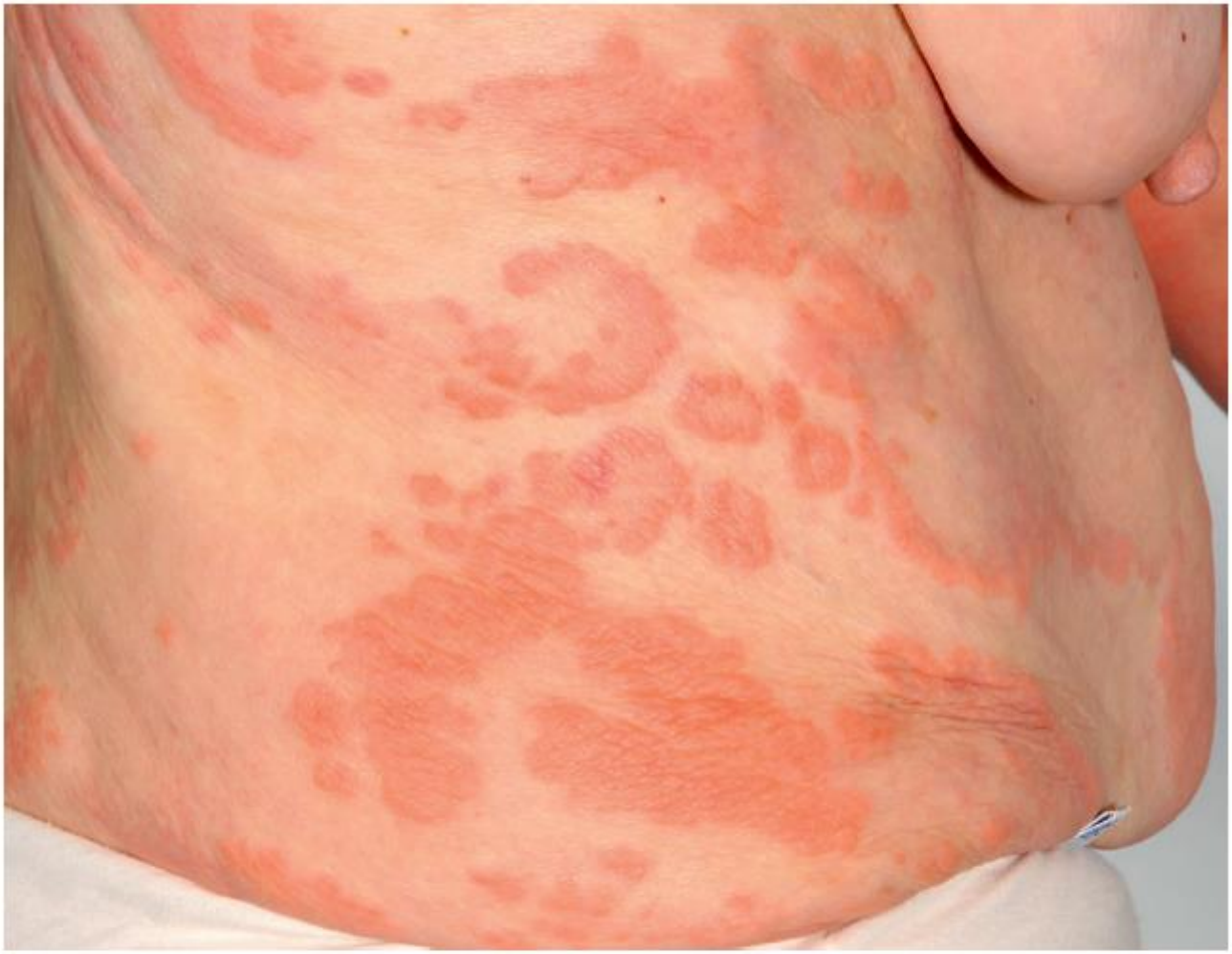


Fig. 30.3 Bullous pemphigoid – urticarial presentation. Multiple, firm annular, arciform and polycyclic urticarial plaques. Note the absence of bullae.

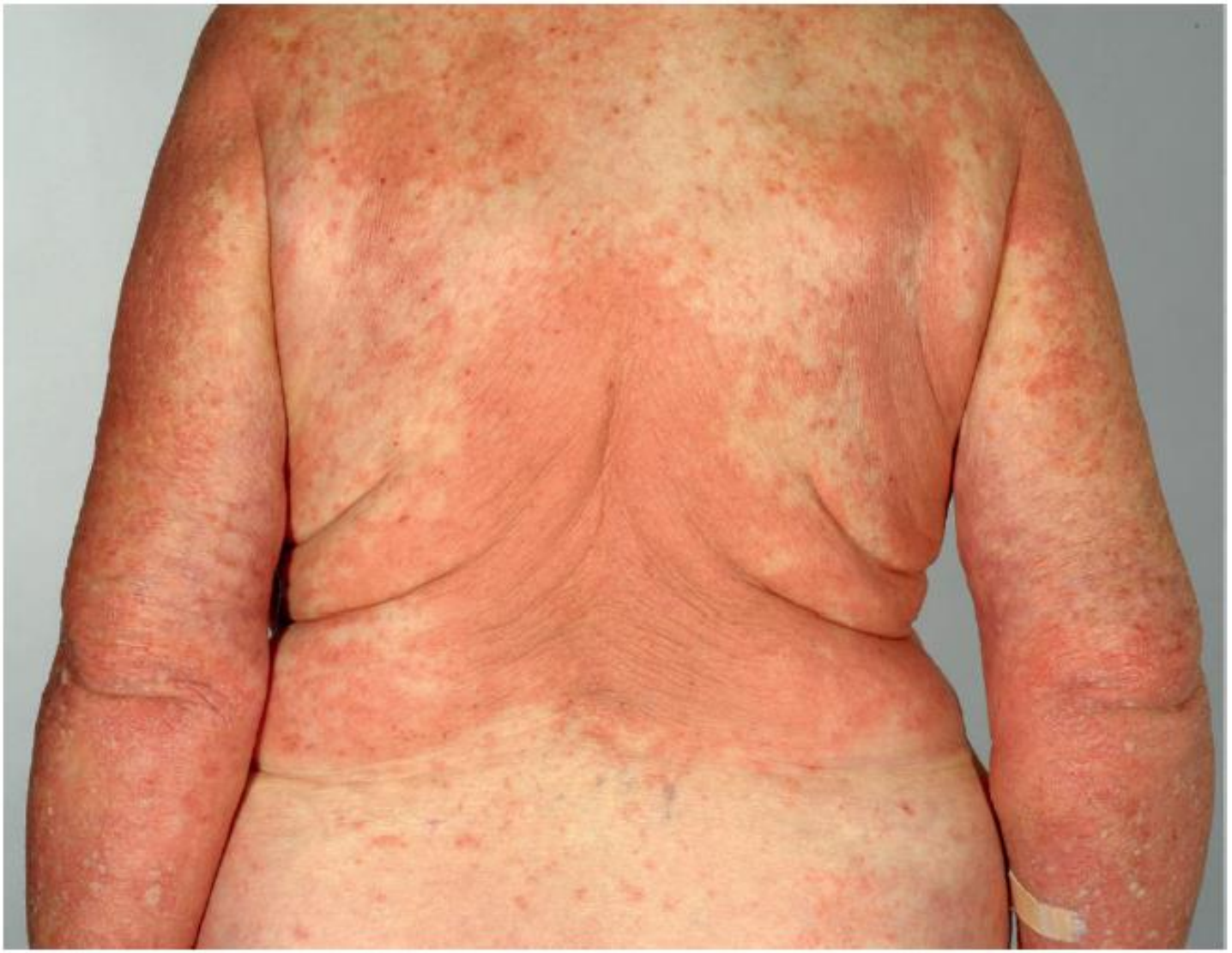


Fig. 30.4 Bullous pemphigoid – eczematous presentation. Large pink eczematous plaques on the trunk and upper

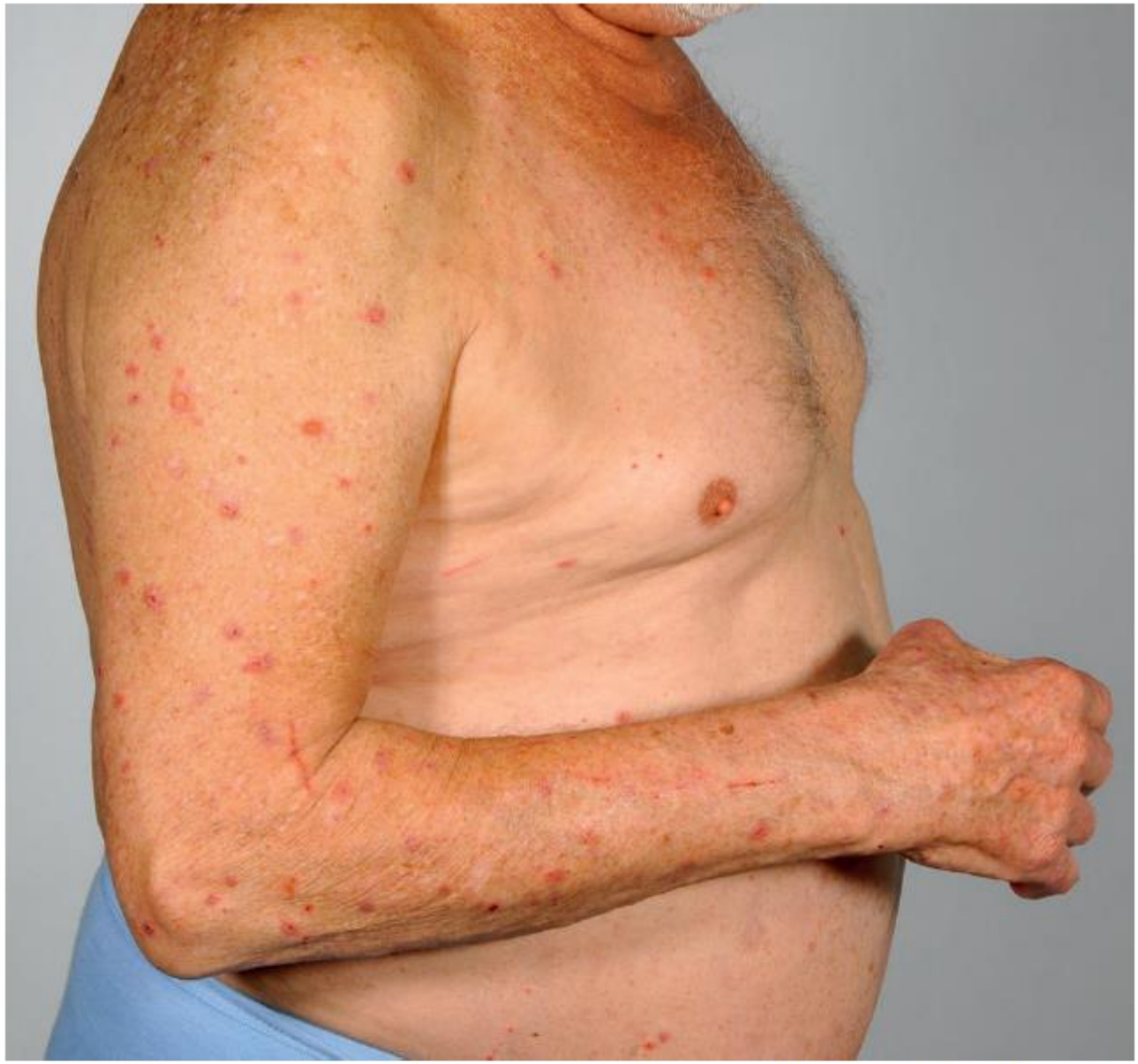


Fig. 30.5 Bullous pemphigoid – nonspecific lesions due to pruritus. Multiple excoriations and nonspecific lesions of prurigo simplex are present. Bullous pemphigoid is in the differential diagnosis of pruritus in the absence of an obvious dermatosis.

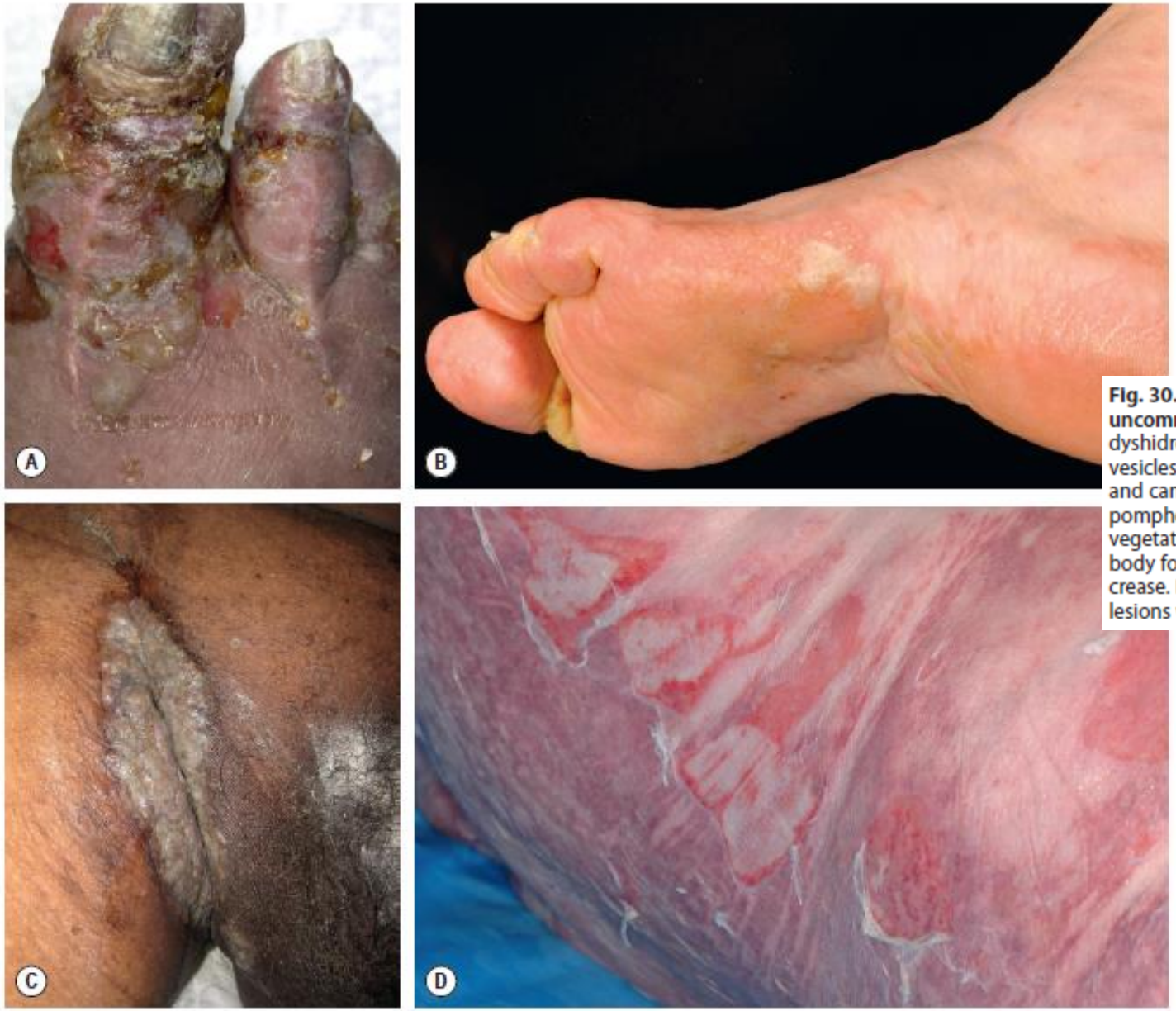


Fig. 30.6 Bullous pemphigoid – uncommon clinical variants. A,B In dyshidrosiform pemphigoid, clusters of vesicles and bullae appear on acral skin and can resemble dyshidrotic eczema or pompholyx. **C** In pemphigoid vegetans, vegetating plaques can develop in major body folds, including the inguinal crease. **D** Toxic epidermal necrolysis-like lesions with large erosions.

Associated Disease

- Malignances → ?
- IBS
- Hashimato thyroiditis
- R.A
- Dermatomyositis
- SLE
- Neurologic disease (Parkinson- dematia)
- MS → Strong association
- After Trauma, Burn, radiotherapy or UV irradiation
- Psoriasis (localize on psoriasis plaque)

Drug Induced BP

- Top of line: Diuretics, Neuroleptics
- NSAID, Antibiotics (Amoxicillin, Cipro)
- ACE inhibitors, TNF-α inhibitors
- Vaccines

UNUSUAL CLINICAL VARIANTS OF BULLOUS PEMPHIGOID

Dyshidrosiform pemphigoid – palmoplantar vesicles and bullae (Fig. 30.6A,B)
Pemphigoid vegetans – intertriginous vegetating plaques (Fig. 30.6C)
Pemphigoid nodularis – prurigo nodularis-like lesions (see Fig. 6.6)
Vesicular pemphigoid – dermatitis herpetiformis-like presentation with small grouped vesicles
Large erosive TEN-like lesions (Fig. 30.6D)
Papular pemphigoid
Eczematous pemphigoid (Fig. 30.4)
Erythrodermic pemphigoid
Lichen planus pemphigoides (see Ch. 11)
Localized lesions:

- pretibial
- vulvar
- peristomal
- umbilical
- distal end of amputated limb*
- paralyzed limb
- sites of radiotherapy†
- Brunsting–Perry form‡

*Also referred to as "stump" pemphigoid.
†Radiotherapy can also provoke generalized form of pemphigoid.
‡Also variant of mucous membrane (cicatricial) pemphigoid.

Table 30.2 Unusual clinical variants of bullous pemphigoid.

Diagnosis

- Clinical presentation
- Histological features
- Direct immunofluorescence (DIF)
- detection of IgG autoantibodies (circulating) (anti-BP180, anti-BP230) or via indirect immunofluorescence (microscopy or ELISA).

Pathology

- Non Bullous early phase: atypical find (eosinophilic spongiosis, dermal infiltration of eosinophil)
- In bulla: subepidermal blister and dermal infiltration of eosinophils and mononuclear cells
- Cavity of bulla (contain net of fibrin and infiltration)

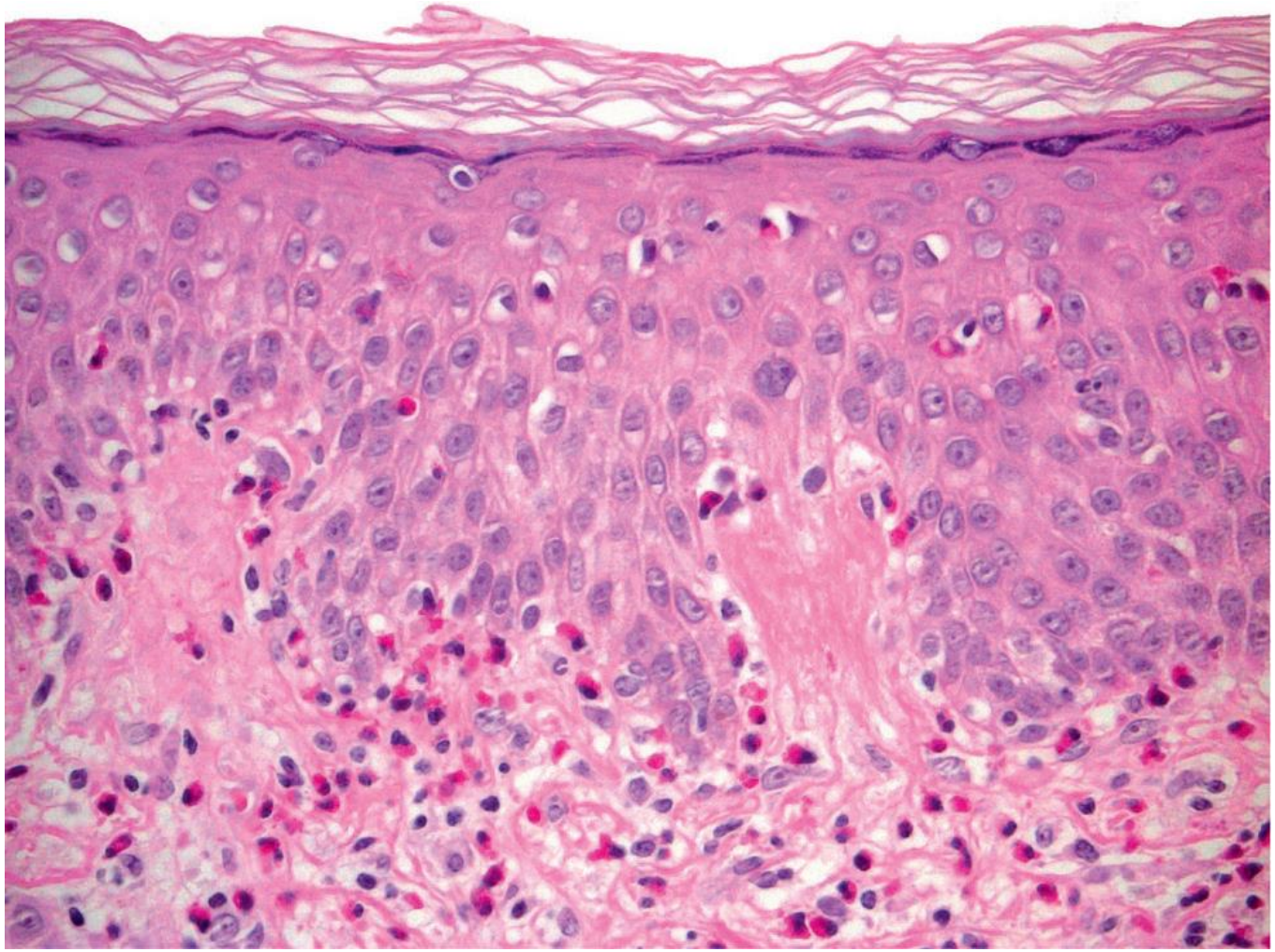


Fig. 30.9 Urticarial phase of bullous pemphigoid – histologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal–epidermal junction, a typical finding in the urticarial stage of BP. *Courtesy, Lorenzo Cerroni, MD.*

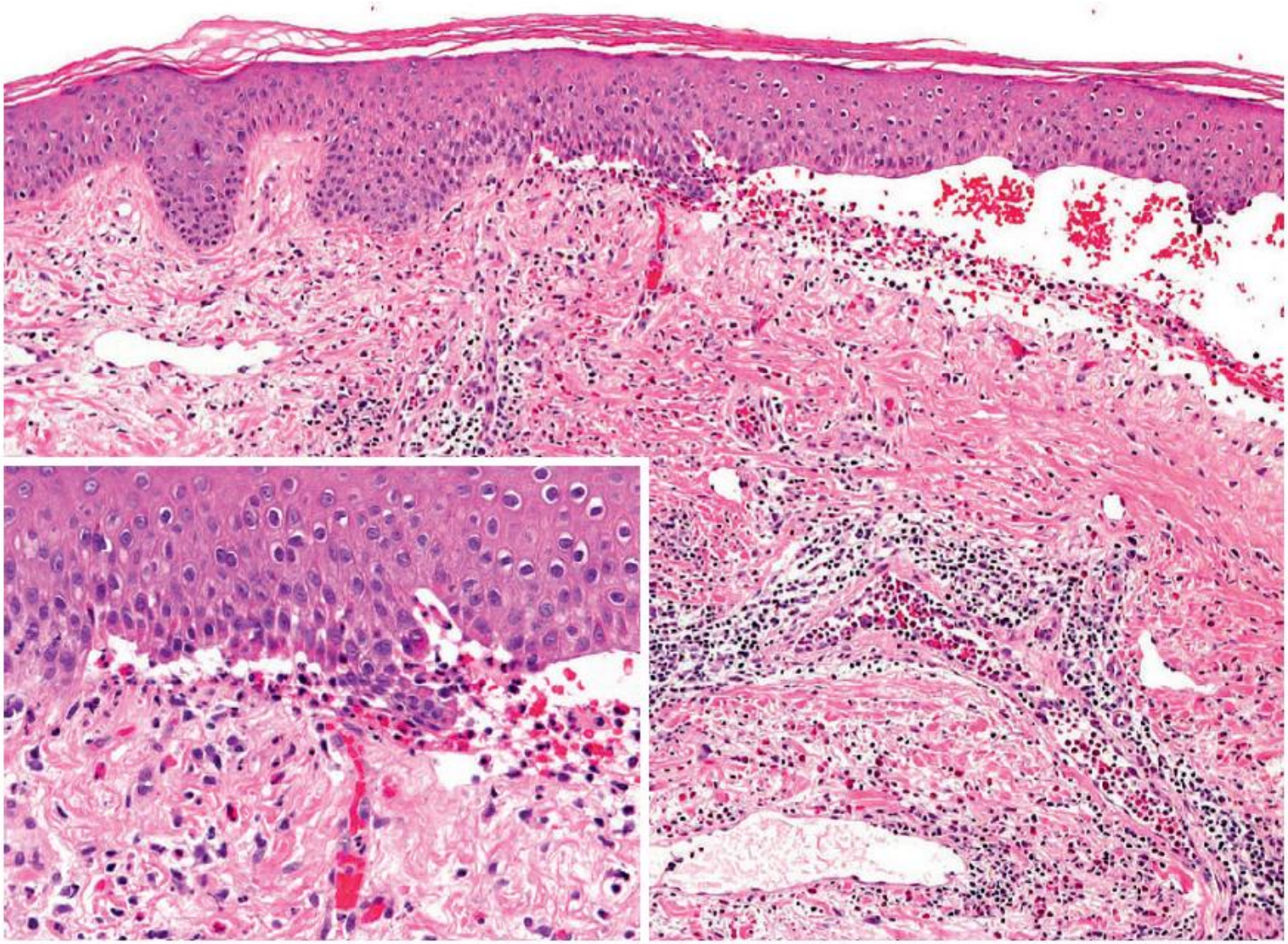


Fig. 30.10 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see inset). *Courtesy, Lorenzo Cerroni, MD.*

DIF microscopy

- In all patients *perilesional*, *uninvolved* skin:
  - Fine, Linear, deposits of IgG (IgG 4, IgG, predominant) and C3
  - Along epidermal basement membrane

Indirect immunofluorescence (IIF) microscopy

- For IIF studies, salt-split normal human skin is choice
- Circulating anti-basement membrane autoantibodies of IgG class (60–80% positive)

ELISA

- Target antigens include BP180 and BP 230
- ≥90% *specific*

Differential Diagnosis

- Drug reaction
- Contact dermatitis
- Prurigo
- Arthropod reactions
- Scabies
- Stevens–Johnson syndrome
- Porphyria
- Dermatitis herpetiformis
- Paraneoplastic pemphigus

Differential Diagnosis…

- in patients with subepidermal Bulla and linear deposition of IgG and C3 along epidermal basement membrane, presence of 4 following criteria strongly indicated BP:

  (1)Absence of skin atrophy;

  (2)Absence of mucosal involvement;

  (3)Absence of head and neck involvement;

  (4)age >70 years

Prognosis

- 30% of patients → relapse during their first year of therapy
- 50% of patients → relapse after stop therapy
- Mortality → in elderly during first year (10% - 40%)

Treatment

THERAPEUTIC LADDER FOR BULLOUS PEMPHIGOID
Mild and/or localized disease
First-line
Superpotent topical corticosteroids (1*)
Second-line
Oral corticosteroids (1)
Minocycline, doxycycline or tetracycline, alone or in combination with nicotinamide (1)
Erythromycin, penicillins (3)
Dapsone, sulfonamides (3)
Topical immunomodulators (e.g. tacrolimus) (3)
Extensive/persistent cutaneous disease
First-line, as primary treatment
Superpotent topical corticosteroids (1*)
Oral corticosteroids† (1‡)
Second-line, or as adjunctive therapy
Azathioprine (2)
Mycophenolate mofetil (2)
Methotrexate§ (2)
Chlorambucil (3)
Cyclophosphamide (3)
IVIg (3)
Plasma exchange (2)
Rituximab (3)
Omalizumab (3)
Immunoadsorption (3)
Note: Superpotent topical corticosteroids should be considered in any patient and may be combined with a systemic therapy.
*Validated.
†Prednisone doses of at least 0.5–0.75 mg/kg/day seem to be necessary to control extensive disease, but increase serious side effects, including mortality. For mild disease, 0.5 mg/kg/day is sufficient.
‡Validated for prednisone.
§In elderly patients, low-dose regimen (2.5–10 mg/wk) can be effective.

Table 30.4 Therapeutic ladder for bullous pemphigoid. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Oral Prednisone

- >10 new blisters/day and inflammatory lesions involve a large body area
- 0.5–1 mg/kg/day
- response: 1 - 2 weeks
- tapered: 6–9 months
- Some authors: taper start once no new lesion or pruritus for at least 2 weeks

Potent Topical Corticosteroids

- Clobetasol propionate 0.05% control disease same oral prednisolone with lower side effect
- Two regim:
  1) 40 g/day
  2) 10–30 g/day
- Occasionally pulse corton (methylprednisolone) required for rapid control of disease.

- Immunosuppressive therapies can serve as steroid- paring agents and are employed when corticosteroids alone fail to control the disease, there are contraindications to the use of systemic corticosteroids, and/or comorbidities exist that limit the dosage of corticosteroid (e.g. diabetes mellitus, osteoporosis, psychosis).

- The most frequently employed agents are azathioprine, mycophenolate mofetil (1.5–3 g/day), methotrexate (7.5–15 mg/week), chlorambucil (2–4 mg/day), and cyclophosphamide.

- The dosage of azathioprine (0.5–2.5 mg/kg/day) should be adjusted according to the level of thiopurine ethyltransferase, in order to increase efficacy and reduce myelosuppression. In the elderly, the dose of methotrexate requires careful monitoring as renal function is often significantly reduced. The choice of a particular immunosuppressive drug depends on its side-effect profile, the patient's overall condition, and the experience of the physician.

THANKS