Indian Association of Dermatologists, Venereologists and Leprologists

Vesiculo-Bullous Disorders

Dr. Sandip Hade
Assistant Professor
Dept of Dermatology
Mimer Medical College, Talegaon Pune

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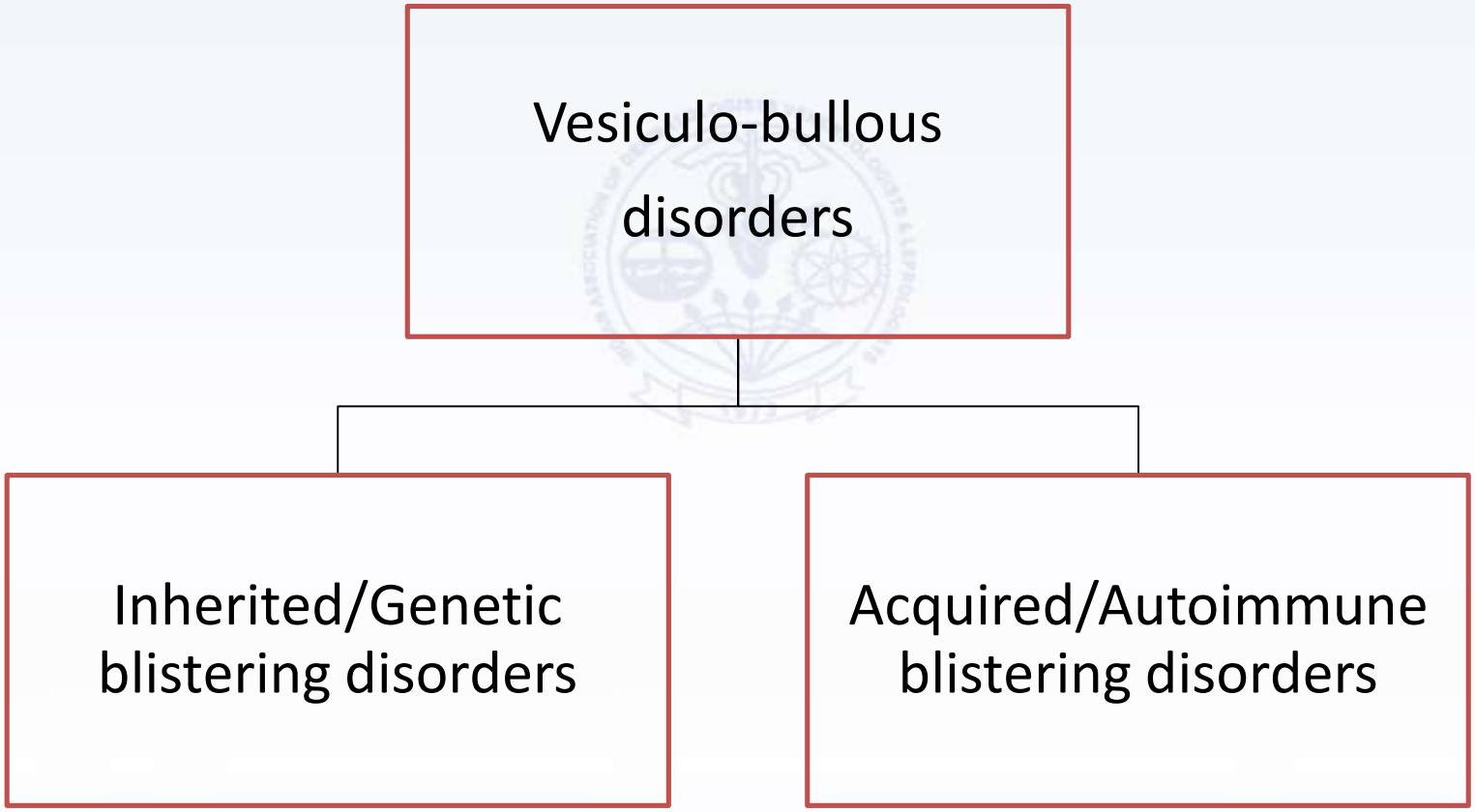
Definitions

Vesiculo-Bullous Disorders :

- Primary event : blistering in the form of vesicle or bullae.
- Vesicles and Bullae - Visible accumulations of fluid within or beneath the epidermis.
  - Vesicles are small, less than 0.5 cm in diameter.
  - Bullae, which may be of any size over 0.5 cm.

- Due to genetic mutation or autoimmune response.
- Pathology : epidermis, dermo-epidermal junction or dermis.

Classification of Vesiculo-bullous Disorders

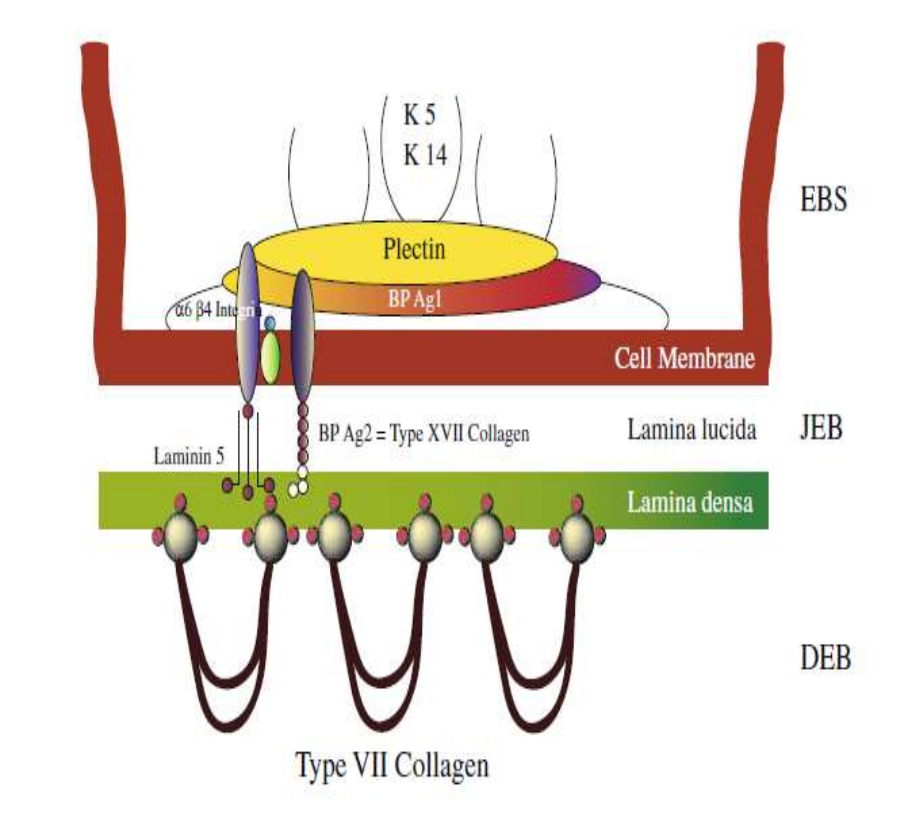


Inherited / Genetic Blistering Disorders
Epidermolysis Bullosa (EB)

- A group of genetic skin disorders - blistering of the skin and mucosae at birth or soon afterwards, following mild mechanical trauma.
- **Mechano-bullous disorders**
- There are three main types of EB :
  - EB simplex (intraepidermal split)
  - Junctional EB (split through the BMZ)
  - Dystrophic EB (split in the subepidermal level)

Basement Membrane Zone (BMZ)/ Dermo-epidermal Junction (DEJ)

- The components of DEJ/BMZ
- Cytoskeleton of basal keratinocytes with hemidesmosome-anchoring filament complexes
- Lamina lucida
- Lamina densa
- Sub-lamina densa



Epidermolysis Bullosa Simplex

- Autosomal dominant inheritance.
- Keratin 5 and 14 mutations resulting in bullae within basal cell keratinocytes.
- Onset of blistering over trauma prone sites at birth or infancy.
- Heal without scarring.
- Mucosa, hair and nails - Spared.

Junctional Epidermolysis Bullosa

- Laminin 5 and bullous pemphigoid antigen 2 (BP180, collagen 17) mutations causing blisters in the lamina lucida
- Autosomal recessive inheritance
- Two forms
  - Lethal - Herlitz type - Laminin 5 mutations
  - Non-lethal - Non-Herlitz type - Laminin 5 or BP180 mutations - Normal life span
- Present at birth or soon afterwards
- Severe skin fragility
- Extensive blistering and denudation
- Teeth - malformed/prematurely lost
- Nails - may be shed

Dystrophic Epidermolysis Bullosa

- Collagen VII mutations - blisters in the sublamina densa.
- AR (more severe) or AD (less severe).
- Skin fragility, scarring with milia.
- Onset at birth or early infancy.
- Blistering of skin mainly over trauma prone sites.
- Oral blisters & scarring - ankyloglossia, microstomia.
- Esophageal lesions - painful dysphagia, strictures.
- Perianal blistering, erosions, scarring - stenosis & fecal retention.
- Eye - symblepharon, corneal erosions, opacity.
- Repeated blistering & progressive scarring - contractures & deformities.

Management of Epidermolysis Bullosa

- **Investigations :**
  - Skin biopsy & electron microscopy – level of split
  - Antigen mapping & immunohistochemistry
  - Prenatal DNA testing for couples at risk of having affected children
- **Treatment :**
  - Avoidance of trauma
  - Maintaining adequate nutrition and hydration
  - Prevention of sepsis
  - Care of the Oral & Ocular mucosa
  - Management of contractures & deformities

Acquired or Autoimmune blistering disorders

Intraepidermal

- Pemphigus foliaceous
- Pemphigus erythematosus
- Endemic pemphigus
- Pemphigus herpetiformis
  Suprabasal blisters
- Pemphigus vulgaris
- Pemphigus vegetans
- Paraneoplastic pemphigus
- IgA Pemphigus – SCD/IEN types

Subepidermal

- Bullous Pemphigoid
- Cicatricial Pemphigoid
- Pemphigoid gestationis
- Linear IgA disease / Chronic Bullous Disease of Childhood
- Dermatitis herpetiformis
- Epidermolysis bullosa acquisita

Pemphigus

- **Pemphigus :** derived from the Greek word “Pemphix” which means blister or bubble.
- **Pemphigus :** a group of autoimmune blistering diseases of the skin and mucous membranes.
- **Histology :** Intra-epidermal blisters due to the loss of cell–cell adhesion & separation of keratinocytes (Acantholysis).
- **Immunopathology :** In-vivo bound & circulating IgG autoantibodies directed against the epidermal cadherins (calcium-dependent cell-cell adhesion molecules) found on the cell surface of keratinocytes.

Pemphigus - Types & Variants

- Pemphigus vulgaris
  - *Variant : pemphigus vegetans*
- Pemphigus foliaceus
  - *Variant : pemphigus herpetiformis*
  - *Variant : pemphigus erythematosus*
  - *Variant : endemic pemphigus*
- Paraneoplastic pemphigus
- Drug-Induced pemphigus
- Intercellular IgA dermatosis
  - *Variant : IgA Pemphigus foliaceus*
  - *Variant : Subcorneal pustular dermatosis*

Pemphigus Vulgaris

Epidemiology

- Disease of middle age. (India-Younger age).
- Ashkenazi Jews - increased susceptibility.
- Male & female - equally affected.

Etiology

- Target antigens: Desmoglien-3 (Desmoglein-1 in few patients).
- Desmoglein - 3 is expressed only in the basal and suprabasal layers of the epidermis
- Desmoglein-1 is found throughout the epidermis, particularly in the upper layers).
- In mucosa, desmoglein-3 is strongly expressed but desmoglein-1 is only weakly expressed.

Pathogenesis

Circulating IgG4 Pemphigus autoantibodies bind to desmoglein-3 & -1 found in desmosomes which are present on the keratinocyte cell membrane

↓

Lysis of intercellular cement substance

↓

Acantholysis

↓

Intra-epidermal blister

Blister cavity consists of mainly acantholytic cells

Pemphigus Vulgaris - Clinical Features

- All patients - Painful erosions of the oral mucosa. Intact blisters are rare in the mucosa because they are fragile and easily breakable.
- >50% of the patients also develop flaccid blisters and widespread cutaneous erosions.
- Thin walled flaccid bullae containing fluid which is initially clear but may become hemorrhagic, turbid, or even sero-purulent.
- Bullae rupture easily to form painful raw surfaces with tendency to spread; long time to heal.
- **Sites :** oral cavity, groins, genitals, axillae, scalp, face, neck.

Pemphigus Vulgaris

Mucosal erosions in Pemphigus vulgaris

Flaccid bullae & erosions

Pemphigus Vulgaris - Clinical Features

- **Nikolsky sign:** lack of cohesion within the epidermis, causes its upper layers easily move laterally with slight pressure or rubbing in active patients with pemphigus.
- **Bulla-spread sign (Asboe–Hansen sign):** gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure, due to the lack of cohesion of keratinocytes.
- Can be fatal due secondary bacterial infections or fluid & electrolyte imbalance (loss of epidermal barrier function).

Bulla-spread sign

Pemphigus Vegetans

- A rare vegetative variant of pemphigus vulgaris.
- Flaccid blisters ⟶ erosions ⟶ fungoid vegetations or papillomatous proliferations,
- Intertriginous areas & scalp, face.
- Tongue : cerebriform-like changes.
- Two subtypes :
  - *Neumann type* - Severe
  - *Hallopeau type* - Mild.

Vegetating plaque in the retro-auricular region

Diagnosis

Tzanck smear

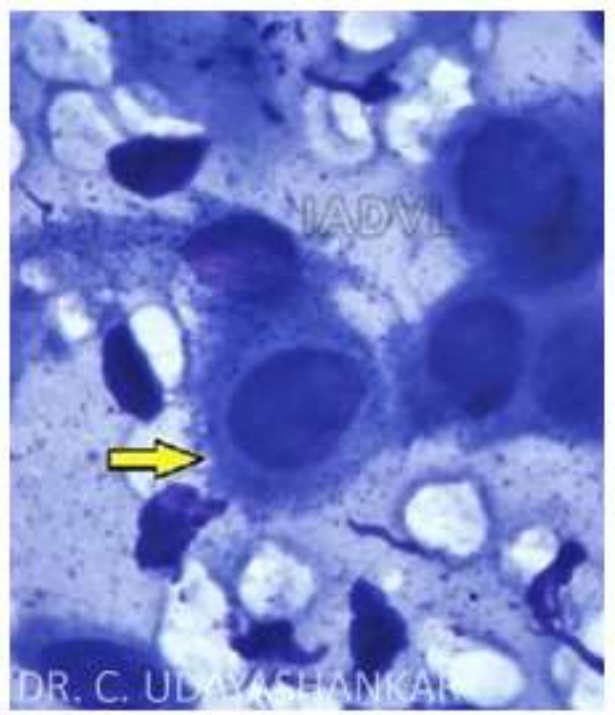
- Acantholytic cell - Large round cell with hyperchromatic nucleus & perinuclear halo due to peripheral condensation of cytoplasm.

Histopathology

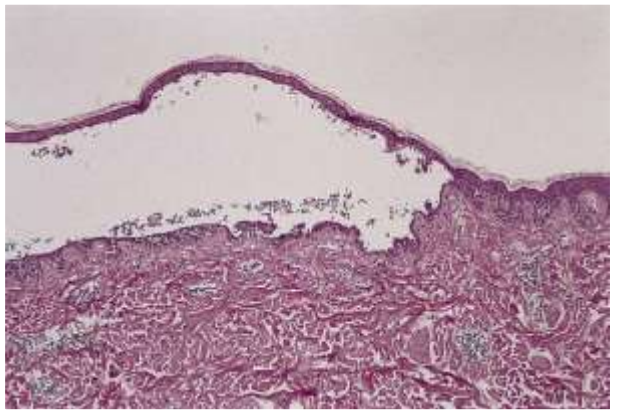
- Supra basal cleft with acantholytic cells.
- Tomb stone appearance.
- Perivascular infiltrate of lymphocytes, neutrophils.

Immunofluorescence

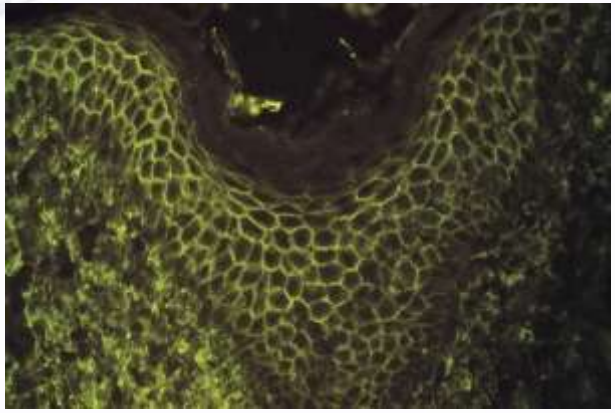
- Intercellular IgG and C3 deposits showing (Fishnet or Honey-comb pattern).



Tzanck smear showing
Acantholytic cells



Suprabasal blister with acantholytic cells in the cleft



DIF showing IgG deposition in the intercellular regions causing the ‘fish-net pattern’.

Treatment of Pemphigus Vulgaris & Its Variants

- Steroids - 1.5-2 mg/kg/day.
- Dexamethasone - Cyclophosphamide pulse (DCP)- 100 mg Dexa in 500 ml of 5% Dextrose on 3 consecutive days, Cyclophosphamide 500 mg IV along with Dexa only on the 1st day. Repeat pulse every 4 weeks.
- Methyl-prednisolone pulse.
- Anti metabolites : Azathioprine, Cyclophosphamide.

Treatment of Pemphigus Vulgaris & Its Variants

- IV Ig – 2g/Kg per cycle divided over 3-5 days
- Dapsone 100-300 mg/d (Steroid sparing agent),
- Nicotinamide 1.5 g/d and Tetracycline 2 g/d combination
- Antimalarials,
- Cyclosporine 3-6 mg/Kg,
- Rituximab-anti-CD20 monoclonal Ab – 375 mg/m2 once a week for 4 weeks.
- Others : Plasmapheresis.

Pemphigus Foliaceus

- Less severe than PV - not severely ill.
- Scaly, crusted cutaneous erosions in a seborrheic distribution (face, scalp and upper trunk) because the vesicle is so superficial and fragile and ruptures easily.
- Do not have clinically apparent mucosal involvement even with widespread disease.
- May stay localized for years or may rapidly progress.
- May produce an erythrodermic exfoliative dermatitis.
- The Nikolsky sign is present.
- Histology : Subcorneal blister with neutrophils in the blister cavity.
- DIF : Intercellular deposition of IgG4 against desmoglein 1

Pemphigus Foliaceus

Scaly crusted erosions in Seborrheic distribution

Subcorneal blistering

Pemphigus Erythematosus (Senear–Usher Syndrome)

- Pemphigus erythematosus - a localized variant of pemphigus foliaceus.
- Typical scaly and crusted lesions- malar region and in other 'seborrheic' areas. Oral mucosa rarely involved.
- Immunologic features of both pemphigus and lupus erythematosus.
- IgG and C3 deposition on cell surfaces of keratinocytes (Pemphigus), granular IgG and C3 on the BMZ, in addition to circulating ANA (LE).
- Associated with myasthenia gravis or thymoma.

Pemphigus Herpetiformis

- Rare and atypical variant of pemphigus.
- Resembles dermatitis herpetiformis in its early phase.
- Widespread clusters of pruritic papules and vesicles develop on an erythematous background.
- Most patients with herpetiform pemphigus have a clinical variant of pemphigus foliaceus and the remainder may have a variant of pemphigus vulgaris.
- Eosinophilic spongiosis & subcorneal pustules without acantholysis histologically;
- IgG autoantibodies directed against the cell surfaces of keratinocytes.
- Target antigen : Dsg1 in most cases & Dsg3 in others.

Endemic Pemphigus Foliaceus
Fogo Selvagem (Wild Fire)

- Endemic to certain parts of South America (Brazil, Columbia etc).
- Common in children and young adults.
- Risk factor - ? Arthropod bite (Black fly - Simuliidae).
- Initial lesions are flaccid bullae. Nikolsky sign +ve.
- Head & neck involved first.
- Burnt appearance & burning sensation - reason for the name Fogo selvagem, Portuguese for ‘wild fire’.
- Mucous membranes - not involved.
- Histologically and immunologically - identical to PF.

Treatment of Pemphigus Foliaceus & Its Variants

- Potent topical or intralesional steroids
- Oral Prednisolone 20-40 mg/day
- Azathioprine
- Cyclophosphamide
- Hydroxychloroquine 200 mg b.i.d.
- IVIg
- Dapsone 100 mg/day

Drug-Induced Pemphigus

- Sporadic cases - associated with the use of drugs, in particular penicillamine and captopril.
- With penicillamine, pemphigus foliaceus is seen more commonly than pemphigus vulgaris.
- Both penicillamine and captopril contain sulfhydryl groups that are speculated to interact with the sulfhydryl groups in Dsg1 and Dsg3.
- May lead to autoantibody production, or may directly interfere with the adhesive function of the desmogleins.
- Most, but not all, patients with drug-induced pemphigus go into remission after the offending drug is discontinued.

Paraneoplastic Pemphigus

- Associated with underlying neoplasms, both malignant & benign.
- Commonly associated neoplasms - NHL, CLL, Castleman's disease, malignant and benign thymomas.
- Earliest presenting sign - Intractable stomatitis, persists and resistant to therapy.
- Most patients - severe pseudo-membranous conjunctivitis which may produce scarring.
- Esophageal, nasopharyngeal, vaginal, labial and penile mucosal lesions may also be seen.
- Polymorphic cutaneous lesions-flaccid or tense bullae, EMF-like . Palms & soles involved (c.f. PV).
- Treatment : Rx of the neoplasm. Usually refractory to all treatments.

IgA Pemphigus

- In middle-aged or elderly.
- **Two types :** the subcorneal pustular dermatosis (SPD) & intraepidermal neutrophilic (IEN).
- In the **SPD type**, IgA autoantibodies - upper epidermal surfaces, while in the **IEN type**, IgA autoantibodies - throughout the entire epidermis.
- Flaccid vesicles or pustules coalesce to form an annular pattern with crusts in the center of the lesion.
- Common sites - axilla and groin. Mucous membrane involvement is rare, pruritus is a significant symptom.
- Immunologic evaluation is essential to differentiate the SPD type from classic subcorneal pustular dermatosis.
- Treatment : Dapsone, Etretinate, Isotretinoin, PUVA, Immunosuppressives, plasmapheresis and Colchicine.

Bullous Pemphigoid

Epidemiology

- Most common subepidermal blistering disorder.
- Disease of the elderly.
- Chronic disease, with spontaneous exacerbations & remissions, with significant morbidity.

Etiology

- Target Antigens : Present in hemidesmosomes which are components of junctional adhesion complexes that promote dermo-epidermal cohesion.
  - BPAg1 or BP230 (230 kDa) &
  - BPAg 2 or BP180 or Type VII Collagen (180 kDa)
- Antibodies : Deposition of IgG, IgA, IgE antibodies & complement along the basement membrane zone.

Pathogenesis of Bullous Pemphigoid

Circulating anti-BP 180 and anti-BP 230 antibodies bind to the target Ags within the DEJ

↓

Activate the complement pathway & release chemoattractants

↓

Recruitment of eosinophils and neutrophils

↓

Release of destructive proteolytic enzymes

↓

BMZ separates

↓

Sub-epidermal blister is formed

Clinical Features of Bullous Pemphigoid

- Cutaneous manifestations - Polymorphic.
- Non-bullous phase - Prodrome for several weeks - Pruritus, eczematous, papular or urticarial lesions.
- Tense vesicles & bullae containing clear fluid on normal or erythematous base → on rupture form denuded areas with tendency to heal spontaneously.
- **Nikolsky's sign :** negative.
- **Sites :** Symmetrical distribution lower abdomen, inner thighs, groins, flexural aspect of limbs. Mucosal surfaces are involved in 10-40% cases.
- **Association :** Malignancy, diabetes, ulcerative colitis, multiple sclerosis.

Bullous Pemphigoid

Tense Bullae

Tense Vesicles

Diagnosis

- **Tzanck smear :** Plenty of eosinophils, few neutrophils but no acantholytic cells.
- **Histopathology :**

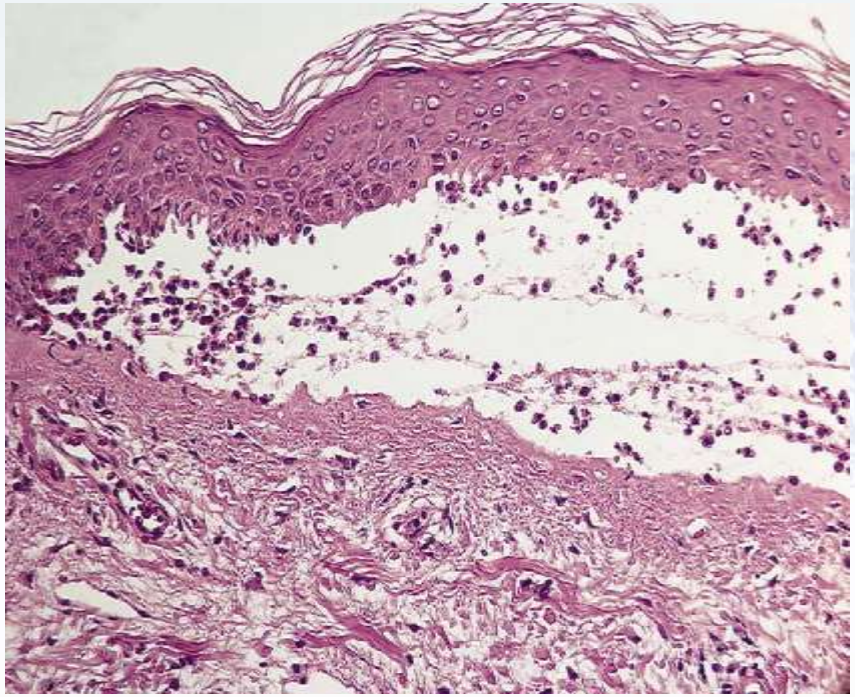
  Epidermis - normal.

  Sub epidermal bulla filled with fibrin and eosinophils.

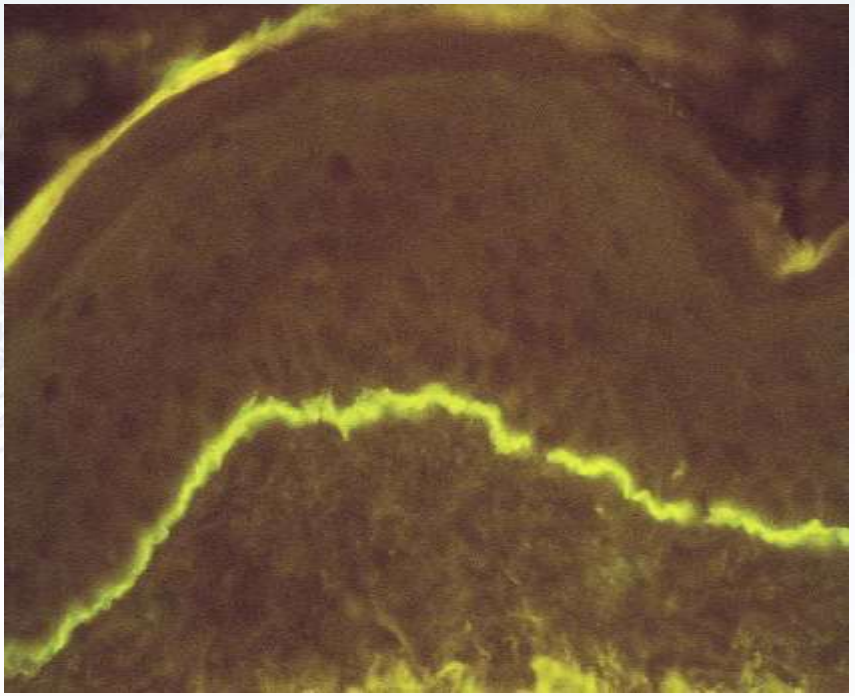
  Dermis shows infiltrate of eosinophils, mononuclear cells and neutrophils.
- **Immunopathology :**

  C3, IgG, IgA, IgM seen along BMZ and in circulation.

Bullous Pemphigoid



Sub-epidermal blister with the lumen containing eosinophils



DIF showing linear C3 deposition at the BMZ

Treatment

- **Topical :** Steroids.
- **Systemic :**

  Steroids 40-80 mg/day & tapered when disease under control

  Dapsone

  Tetracycline and Nicotinamide

  Immunosuppressants

  Plasmapheresis & IV Gamma globulins
- **Prognosis :**
  - Benign self limiting disease lasting from months to years.
  - Mortality rate less after advent of steroids.
  - Most common cause of death is usually some underlying associated disease.

Cicatricial Pemphigoid

- Rare blistering disorder, results in permanent scarring of the affected area.
- Mucosal lesions predominate-oro-pharynx, nasopharynx, conjunctiva, larynx, genitalia & esophagus.
- Sequelae include oropharyngeal adhesions, esophageal strictures, stridor, introital shrinkage, symblepharon and ‘statue eye’.
- Histology: Subepithelial bullae, similar to BP.
- DIF : Linear C3, IgG, fibrinogen, occasionally IgM/IgA at basement membrane in 90%.
- IIF : linear at basement membrane in 20%.

Herpes Gestationis

- Autoimmune blistering disease of young women.
- Occurs in pregnancy (21–28 weeks of gestation) or within 1st week postnatally.
- Starts as severe pruritus with urticarial wheals and plaques followed by blistering predominantly in the periumbilical area, lower abdomen and thighs.
- Mucosal involvement - rare.
- Lesions improve postpartum.
- Recurrence may occur in subsequent pregnancies, premenstrually or with oral contraceptive pills (OCPs).
- Direct immunofluorescence shows linear C3 deposits at the BMZ with IgG in some cases.

Linear IgA Disease

- Acquired subepidermal blistering disorder of children & adults, with skin & mucous membrane involvement.
- Characterized by linear deposition of IgA at basement membrane zone.
- It consists of two main entities
  - Chronic Bullous Disease of Childhood (CBDC) &
  - Linear IgA disease.
- Overlap in the clinical presentation of the two entities but they differ in age at presentation and few clinical signs.
- Periorificial and annular lesions are more common in CBDC than in linear IgA disease.

Linear IgA Disease

Tense bullae

String of pearl appearance

Chronic Bullous Disease of Childhood (CBDC)

- Autoimmune sub-epidermal blistering disease of children characterized by IgA BMZ antibodies.
- Onset is usually at around 5 years of age.
- Urticarial plaques with blistering at the edges – 'string of pearls' appearance and localization of lesions around orifices (perioral, perigenital).
- Spontaneous remission usually occurs with age.
- Direct immunofluorescence shows linear IgA at BMZ.
- Treatment :

  Dapsone is usually effective (response usually occurs within 24-48 hours), and may be combined with low dose steroids in refractory cases.

CBDC

Bullae In Circular (Annular) Arrangement

Dermatitis Herpetiformis (DH)

- Intensely pruritic, chronic, recurrent, papulovesicular disease.
- Underlying gluten-sensitive enteropathy - may be asymptomatic.
- Onset usually between 20-55 Years.
- Mainly males.
- External factors: Gluten containing diet like wheat, barley, oats and rye.
- Antigen: Gut epithelial antigen cross reacts with skin
- Antibodies: IgA directed against gliadin and autoantigens like reticulin and endomysium
- C3, IgG, IgM may be seen

Dermatitis Herpetiformis (DH)

- Pruritus - first & predominant symptom.
- Symmetrical eruption of grouped erythematous papules and papulovesicles ⟹ rapidly excoriated - intact vesicles are difficult to demonstrate.
- Extensor aspects of limbs (elbows and knees), buttocks, natal cleft, shoulders, upper back , face and scalp.
- Oral lesions are common but asymptomatic.
- Provocation of lesions occurs with iodides.
- **Differential Diagnosis :**

  Scabies, Prodromal phase of Bullous pemphigoid, prurigo, papular urticaria, neurotic excoriations etc.

Dermatitis Herpetiformis

Symmetric, grouped papulovesicles on the elbows

Excoriations and post-inflammatory changes

Management of DH

Investigation

- Histology of intact vesicles reveals neutrophilic microabscesses at the tips of dermal papillae.
- Direct immunofluorescence on clinically normal skin (buttocks) - granular IgA deposits in dermal papillae.

Treatment

- Strict gluten free diet
- Dapsone 100-200 mg/day
- Sulphapyridine 1.5 g/ day
- Tetracycline with nicotinamide
- Colchicine when the above drugs are contraindicated

Epidermolysis Bullosa Acquisita (EBA)

- Autoimmune disorder of the elderly.
- Trauma-induced subepidermal blistering or a clinical picture indistinguishable from bullous pemphigoid.
- Sub epidermal blistering on histopathology.
- Tissue bound & circulating IgG anti bodies to type VII collagen (major component of anchoring fibrils in the BMZ).

The antigen-antibody complex cause.

- Direct destruction of anchoring filaments (non-inflammatory type)
- Inflammatory response via complement system activation (inflammatory type).

This causes the BMZ split and thus a sub epidermal blister.

Clinical features

- 4th to 6th decade, M=F

Non-Inflamatory type

- Flaccid blisters over the trauma prone areas
- Heal with scarring, milia and hyperpigmentation
- Cicatricial alopecia and dystrophic nails seen

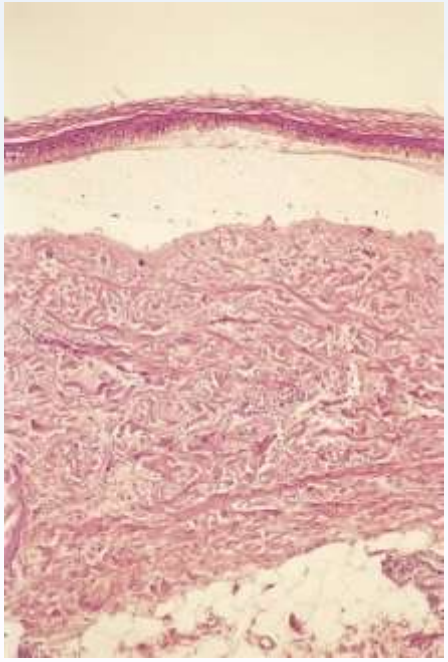
Inflammatory type

- Tense blisters and urticarial plaques on erythematous base that heal without scarring
- **Sites :** Dorsa of hands and feet, elbows, knees
- **Associations :** SLE, inflammatory bowel disease

Diagnosis

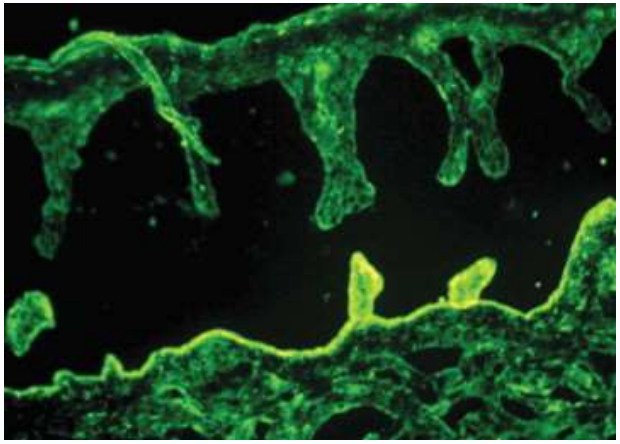
Histopathology

- Sub-epidermal blister with or without neutrophilic infiltrate



Immunopathology

- Linear deposition of IgG, C3 and sometimes IgM, IgA
- Salt - splitting technique : Antibodies on dermal side



Treatment

- Supportive therapy
- Steroids in combination with dapsone/ sulphonamides/ Azathioprine/ Methotrexate
- Colchicine
- Cyclosporine
- IV immunoglobulin

Prognosis

- Chronic protracted disease with remission and exacerbations
- Inflammatory type is amenable to treatment
- Non-inflammatory type is difficult to suppress
- Rarely the disease may remit spontaneously

Approach to vesiculobullous disorders

- **Clinical history** and classical features.
- **Age** of onset and family **history** and drug history : Hereditary or acquired or drug-induced.
- **Nature of the bullae :** Flaccid - Intraepidermal; Tense - Subepidermal.
- **Bulla spread sign and Nikolsky sign** - to look for acantholysis.
- **Tzanck smear :** To look for acantholytic cells, eosinophiols, neutrophils.
- **Histopathology :** to find out the level of blister and type of cellular inflammatory infiltrate.
- **Immunofluorescence :** both direct and indirect methods for autoimmune bullous dermatoses.

MCQs

Q.1) Nikolsky sign is commonly negative in?

A. Bullous Pemphigoid
B. Pemphigus vulgaris
C. Pemphigus foliaceus
D. Toxic epidermal necrolysis

Q.2) Drug of choice in the treatment of dermatitis herepetiformis is?

A. Prednisolone
B. Mycophenolate mofetil
C. Dapsone
D. Azathioprine

MCQs

Q.3) Row of tomb stone appearance on histopathology is seen in?

A. Epidermolysis bullosa dystrophica
B. Cicatricial Pemphigoid
C. Chronic bullous disease of childhood
D. Pemphigus vulgaris

Q.4) Dystrophic Epidermolysis bullosa is due to mutations in?

A. Laminin 5
B. BPAg 2(BP180, collagen 17)
C. Keratins 5 & 14
D. Type VII Collagen

MCQs

Q.5) Senear-Usher syndrome is

A. Bullous Pemphigoid

B. Pemphigus erythematosus

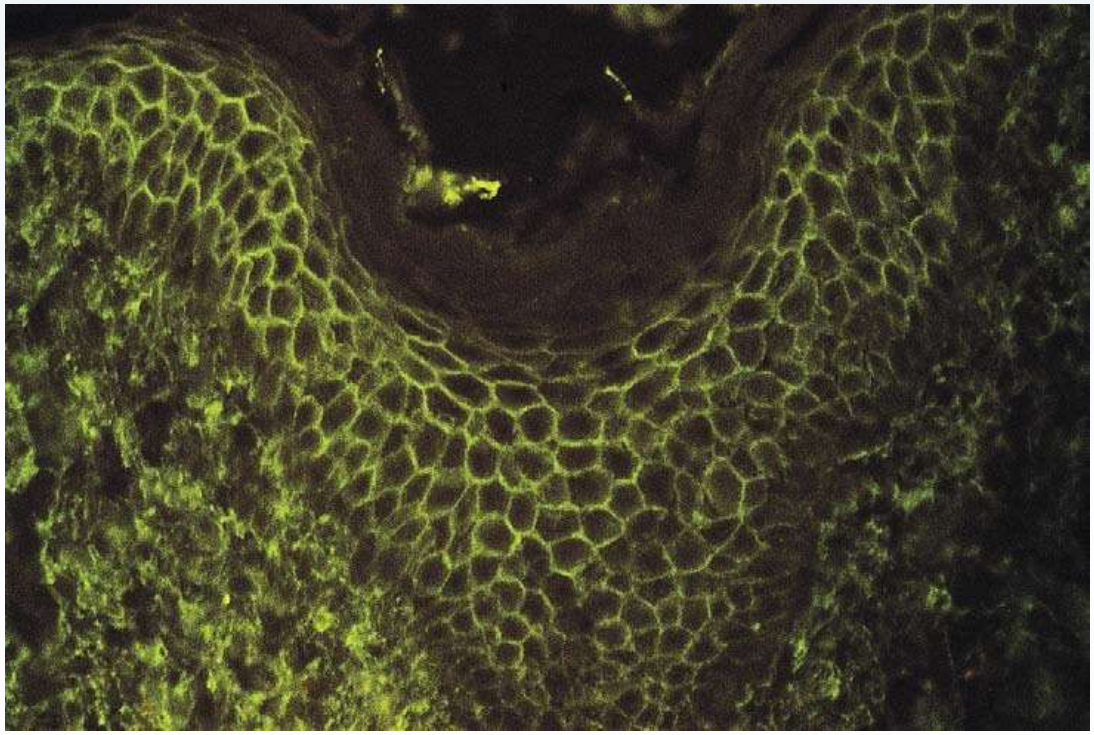
C. Pemphigus herpetiformis

D. Linear IgA disease

Photo Quiz

Q. Identify the vesicullobullous disorder and describe the skin lesions.

Photo Quiz



Q. Identify the immunofluorescence pattern.

Thank You!