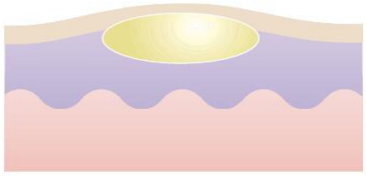
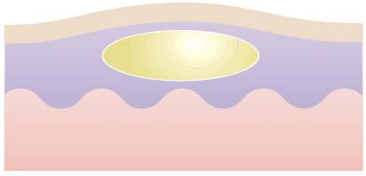
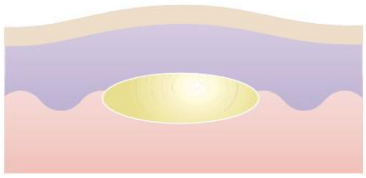
Dermatology. **Lecture: 8**
Dr. Intisar Ahmed **Stage: 5**

Bullous disease

*Vesicles and bullae: are accumulations of fluid within or under the epidermis.
*The appearance of a blister is determined by the level at which it forms;
-Subepidermal blisters: occur between the dermis and the epidermis, their roofs are thick and tend to be tense and intact.
-Intraepidermal blisters: appear within the prickle cell layer of the epidermis, and so have thin roofs and rupture easily to leave an oozing denuded surface.
*This tendency is even more marked with subcorneal blisters, which form just beneath the stratum corneum and therefore have even thinner roofs.

Location of bullae	Diseases
 Subcorneal bulla	Bullous impetigo Miliaria crystallina Staphylococcal Scalded skin syndrome
 Intraepidermal bulla	Acute eczema Viral vesicles Pemphigus Miliaria rubra Incontinentia pigmenti
 Subepidermal bulla	Bullous pemphigoid Cicatricial pemphigoid Pemphigoid gestationis Dermatitis herpetiformis Linear IgA disease Bullous erythema multiforme Bullous lichen planus Bullous lupus erythematosus Porphyria cutanea tarda Toxic epidermal necrolysis Cold or thermal injury Epidermolysis bullosa

Bullous disorders of immunological origin

Many chronic bullous diseases are caused directly or indirectly by antibodies binding to normal tissue antigens.

The Pemphigus family

Pemphigus is often severe and potentially life threatening.

Types:

- Pemphigus **vulgaris**, include pemphigus vegetans.
- Pemphigus **foliaceus**, include pemphigus erythematosus (localized).
- Herpetiform pemphigus
- **Drug**-induced pemphigus, eg/ penicillamine and ACE inhibitors.
- **Paraneoplastic** pemphigus, eg/ thymoma, Castleman'stumour, lymphoma.
- **IgA** pemphigus.

Cause

*All types of pemphigus are autoimmune diseases in which pathogenic *immumoglobulin G antibodies* bind to antigens within the epidermis.

*The main target antigens are *desmoglein 3 (in pemphigus vulgaris)* and *desmoglein 1 (in superficial pemphigus).*

*Both desmoglein 3 and desmoglein 1 are cell-adhesion molecules found in desmosomes.

*The antigen–antibody reaction interferes with adhesion, causing keratinocytes to fall apart (acantholysis).

Presentation

*Pemphigus vulgaris is characterized by flaccid blisters of the skin and mouth.

*The blisters rupture easily to leave widespread painful erosions.

*Most patients develop the mouth lesions first.

*Shearing stresses on normal skin can cause new erosions to form (a positive **Nikolsky sign**).

*In the **vegetans** variant heaped up cauliflower-like weeping areas are present in the groin and body folds.

*The blisters in pemphigus **foliaceus** are so superficial, and rupture so easily,that the clinical picture is dominated more by weeping and crusted erosions than by blisters. In the rarer pemphigus **erythematosus** the rash may have a predilection for photoexposed areas; on the face, lesions are often pink, rough and scaly.

Course

*The course of all forms of pemphigus is prolonged, even with treatment, and the mortality rate is **15%.**
*The cause of death:
1. Infection.
2. Side effects from systemic corticosteroids.
*Superficial pemphigus is less severe.
*With modern treatments, most patients with pemphigus can live relatively normal lives, with occasional exacerbations.

Differential diagnosis

-Widespread erosions: pyoderma, impetigo, epidermolysis bullosa or ecthyma.
-Mouth ulcers: aphthae, Behc¸et's disease or herpes simplex infection.
-Scalp erosions: bacterial or fungal infections.
*Pemphigus erythematosus is now considered as an overlap syndrome with lupus erythematosus.

Investigations

-Biopsy: shows that the vesicles are intraepidermal, with rounded keratinocytes floating freely within the blister cavity (acantholysis).
-Direct immunofluorescence of adjacent normal skin shows intercellular epidermal deposits of IgG and C3.
-ELISA: assays can also be used to confirm the diagnosis, the titre of these antibodies correlates loosely with clinical activity and may guide changes in the dosage of systemic steroids.

Treatment

1.Resistant and severe cases need very high doses of systemic steroids, such as prednisolone 60–180 mg/day.
The dose is reduced only when new blisters stop appearing.
2.Immunosuppressive agents, such as azathioprine, cyclophosphamide and mycophenylate mofetil, are often used as steroid-sparing agents.
3.With long-term corticosteroid therapy so consider bone and gastric protection.
4.Plasmapheresis.
5.Intravenous immunoglobulin.
6.Rituximab is a humanized murine monoclonal antibody to CD20 on B cells.
7.Dapsone may sometimes be helpful, especially to allow healing.
*After control has been achieved, prolonged maintenance therapy and regular follow-up will be needed.

*In superficial pemphigus, smaller doses of systemic corticosteroids are usually needed, and the use of topical corticosteroids may help too.

The Pemphigoid family

Bullous pemphigoid is an autoimmune disease.
*The main target antigen is within basement membrane zone.
*The IgG antibodies bind to two main antigens: most commonly to **BP230 and less often to BP180.**
*Complement is then activated starting an inflammatory cascade.
*Eosinophils often participate in the process causing the epidermis to separate from the dermis.

Presentation

*Bullous pemphigoid is a chronic, usually itchy, blistering disease, mainly affecting the elderly (mean age of onset around 80 years).
*Usually, no precipitating factors can be found, but rarely drugs, ultraviolet radiation exposure or radiotherapy seem to play a part.
*Several neurological diseases may pre-date the onset of the disease; including cerebrovascular disease, Parkinson's disease, epilepsy and multiple sclerosis, and these are now considered risk factors for bullous pemphigoid.
*The skin often erupts with smooth itching red plaques in which tense vesicles and bullae form. Or they arise from normal skin.
*The flexures are often affected; the mucous membranes usually are **not**.
*The Nikolsky test is **negative**.
*The disorder would not be fatal, factors carrying a high risk include old age, the need for high steroid dosage, and low serum albumin levels.

Course

*Bullous pemphigoid is usually self-limiting and treatment can often be stopped after 1–2 years.

Differential diagnosis

-Epidermolysis bullosa acquisita,
-Bullous lupus erythematosus,
-Dermatitis herpetiformis,
-Pemphigoid gestationis,
-Bullous erythema multiforme and linear IgA bullous disease.

Investigations

-Biopsy: subepidermal blister is often filled with eosinophils.
-Direct immunofluorescence shows a linear band of IgG and C3 along the basement membrane zone.
-Indirect immunofluorescence, using serum patient, identifies IgG antibodies that react with the basement membrane zone.
-Most patients have peripheral blood eosinophilia.

Treatment

1. Mild bullous pemphigoid can sometimes be controlled by the use of very potent topical steroids alone.
2. In acute phase, prednisolone at a dosage of 40–60mg/day is usually needed. The dosage is reduced as soon as possible, and patients end up on a low maintenance regimen of systemic steroids, taken on alternate days until treatment is stopped.
3. Anti-inflammatory antibiotics and/or nicotinamide may confer further benefit.
4. For non-responsive disease, immunosuppressive agents such as azathioprine, methotrexate or dapsone may be required.
5. Again, if longterm corticosteroid therapy is required bone and gastric protection should be considered.

Pemphigoid gestationis (herpes gestationis)

*This is pemphigoid occurring in pregnancy, or in the presence of a hydatidiform mole or a choriocarcinoma.
*Certain paternally derived histocompatability antigens carried by the fetus might provoke an autoimmune response directed towards BP180 in the skin of some mothers.
*Clinically, pruritic papules and plaques are found in a peri-umbilical distribution; less common are the typical tense bullae found in bullous pemphigoid.
*The condition usually remits after the birth but may return in future pregnancies.
*Treatment
-Topical or systemic steroids.
-Oral contraceptives should be avoided, because their hormones may precipitate the disease.

Dermatitis herpetiformis

*Is a very itchy chronic subepidermal vesicular disease, in which the vesicles erupt in **groups** as in herpes simplex –hence the name herpetiformis.
*Has a male preponderance.

Cause

*Gluten-sensitive enteropathy (sprue, adult coeliac disease), is always present, but most patients do not have symptoms (diarrhoea, constipation or malnutrition) as the enteropathy is mild, patchy and involves only the proximal small intestine.
*Antibodies directed against tissue transglutaminase, reticulin, gliadin and endomysium –a component of smooth muscle.
*IgA antibodies against tissue transglutaminase cross-react with antigens of epidermal transglutaminase leading to granular deposits of IgA in the tips of the dermal papillae and along the basement membrane.
*These induce neutrophil-rich inflammation, which separates the epidermis from the dermis (subepidermal cleft). The IgA deposits in skin clear slowly after the introduction of a gluten-free diet.

Presentation

*The extremely itchy, grouped vesicles and urticated papules develop in a symmetrical distribution over the elbows, knees, buttocks and shoulders.
*They are often broken by scratching before they reach any size, therefore a typical patient shows only grouped excoriations and erosions.
*Sometimes, a secondary eczematous dermatitis develops from scratching, Thus the name dermatitis comes from scratching, and herpetiformis comes from grouping of vesicles and crusts.

Course

*The condition typically lasts for decades unless patients avoid gluten entirely.

Complications

-Diarrhoea,
-Abdominal pain,
-Anaemia,
-Malabsorption.
-Small bowel lymphomas have been reported, and the use of a gluten-free diet may reduce this risk.
*There is a proven association with other autoimmune diseases, most commonly of the thyroid.

Differential diagnosis

-Linear IgA bullous disease,
-Scabies,
-Excoriated eczema,

-Insect bites or neurodermatitis.

Investigations

-Biopsy for vesicle, show subepidermal blister, with neutrophils packing the adjacent dermal papillae.
-Direct immunofluorescence of uninvolved skin shows granular deposits of IgA, and C3, in the dermal papillae and superficial dermis.
-Serum antibody tests for antiendomysial antibodies or tissue transglutaminase can help diagnose the enteropathy.
-Small bowel biopsy is no longer recommended as routine because the changes are often patchy.

Treatment

1.Gluten-free diet.
1.Dapsone or sulfapyridine, both can cause severe rashes, haemolytic anaemia (especially in those with glucose-6-phosphate dehydrogenase deficiency), leucopenia, thrombocytopenia, methaemoglobinaemia and peripheral neuropathy. *Regular blood checks are therefore necessary.

Table 9.1 Distinguishing features of the three main immunobullous diseases.

	Age	Site of blisters	General health	Blisters in mouth	Nature of blisters	Circulating antibodies	Fixed antibodies	Treatment
Pemphigus	Middle age	Trunk flexures and scalp	Poor	Common	Superficial and flaccid	IgG to intercellular adhesion proteins	IgG in intercellular space	Steroids Immunosuppressives
Pemphigoid	Old	Often flexural	Good	Rare	Tense and blood-filled	IgG to basement membrane region	IgG at basement membrane	Steroids Immunosuppressives
Dermatitis herpetiformis	Primarily adults	Elbows, knees, upper back, buttocks	Itchy	Rare	Small, excoriated and grouped	IgG to the endomysium of muscle	IgA granular deposits in papillary dermis	Gluten-free diet Dapsone Sulphapyridine