Blistering diseases

Autoimmune blistering conditions, or bullous skin diseases, the most typical kind of autoimmune diseases that affect the skin proteins that hold an individual's skin cells together are attacked by the immune system.
There are many oral diseases with blistering forms. Blister can be: small and large Vesicle Bulla Can be: intraepithelial and subepithelial
Epithelial Biology

Epithelium has a complex structure and many protein molecules required for epithelial integrity.

The oral epithelium keratinocytes adherent to each other by desmosomes and via hemidesmosomes to the basal membrane and the underlying lamina propria and dermis.
Three-dimensional view of desmosome

- Plasma membranes of adjacent cells
- Anchoring proteins in each cell
- Membrane proteins that link cells
- Intermediate filaments
Hemidesmosomes

- Intermediate filaments
- BP230
- Plectin
- BP180
- α6 integrin
- β4 integrin
- Laminin
- Extracellular matrix
proteins that hold an individual’s skin cells together can be attacked by the immune system.
AUTOIMMUNE SKIN DISEASES

B cell Antibody mediated

Blistering diseases

Intraepithelial Pemphigus

Subepithelial Pemphigoid/EBA/LABD

T cell

Connective tissue diseases, GVHD

B and T cell

Paraneoplastic pemphigus CTD-associated vasculitis
Main types of Pemphigus with oral involvement

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PEMPHIX – BLISTER

- It is a term derived from the Greek language.
- It means blister or bubble.
- A group of potentially life-threatening autoimmune, mucocutaneous diseases.
- Characterized by intraepithelial or subepithelial blistering affecting the skin and/or mucosal surfaces.
- 0.1-0.5/100 000 people become ill in this disease yearly.
Pemphigus group Vulgaris (PV)

This is the most frequent form of PV on the skin and mucous membranes causing blisters, ulcers or erosions on the skin and mucous surfaces.

The IgG type autoantibody is produced against CADHERIN, an adhesion molecule.

Desmoglein1 in the skin
Desmoglein3 (Dsg) in the mucous membrane.
Oral mucosal symptoms

On the oral mucosa a 130 kD molecule Dsg3
Damage of the intercellular area leads to the separation of keratinocytes, which is the so-called ACANTHOLYSIS typical in Pemphigus.
Direct immunofluorescent techniques indicating the auto IgG
GENETIC background

Strong genetic background of PV certain ethnic groups Ashkenazi Jews South Asian Mediterranean origin. Association of Pemphigus with HLA-II class are found in HLA-DR4 and HLA-DBQ1. Japanese PV patients with pemphigus Asian alleles HLA-B15 significantly increased.
In pemphigus vulgaris,

- Oral lesions occur in most patients.
- Oral lesions are usually first to surface and last to resolve in any given patient.
- In some patients, it remains exclusively an oral disease for months or years before generalized skin disease develops.
ORAL MANIFESTATIONS OF AUTOIMMUNE BLISTERING DISEASES

- It can affect any area of the oral cavity: gingiva, palate, buccal, tongue, floor of the mouth, and pharynx.
- Blisters are broken easily; they rarely are observed clinically.
- Instead, erosions and superficial ulcers more likely are observed.
antibodies are deposited intercellularly directed against the extracellular domains of **Dsg3**, by this way oral lesions appear at an early stage.

**Development of Dsg1 autoantibody** in Pemphigus Vulgaris correlates with the disease progression involvement of skin and mucosa other than oral.
Blisters in pemphigus vulgaris are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules.

- Antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane.

- The binding of autoantibodies results in a loss of cell-to-cell adhesion, acantholysis.

- The antibody alone is capable of causing blistering without complement or inflammatory cells.
Antibodies

- Antidesmoglein 1
- and antidesmoglein 3 Ig
- immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses.
- Disease activity correlates with antibody titers
- Lack of in vivo antibody binding (reversion to a negative result on direct immunofluorescence) is the best indicator of remission
Association with other autoimmune diseases

- Rheumatoid Artheritis
- Systemic Lupus Erythematosus
- Myasthenia Gravis
- Pernicious type Anemia

Möller-Hunter glossitis
Drug-induced pemphigus vulgaris

- Might trigger pemphigus vulgaris:
  - Drugs associated with PV:
    - penicillamine,
    - captopril,
    - cephalosporin,
    - pyrazolones,
    - nonsteroidal anti-inflammatory drugs (NSAIDs),
    - other thiol-containing compounds.

- Emotional stress,
- Thermal burns,
- Ultraviolet rays,
- Infections:
  - coxsackievirus,
  - herpesvirus
Risk Factors

- **Diet:** Garlic associated with cases of P.V.
- **Drugs:**
  - a. sulphhydrl radicals (thiol or SH containing penicillamine and captopril,
  - b. drugs with amin-group in their molecule (rifampicin, diclophenac)
- **Viruses:** HHV8 has a tropism to epithelial cells

**Other factors:**
Recent multicentric studies revealed

- lower number of smokers among the PV patients
- higher exposure rates to pesticides
- higher number of females who had been pregnant
- contribution of oestrogenes in the disease process
Pemphigus in the oral cavity
Diagnosis and Treatment

It is crucial to establish the diagnosis of P.V. as early as possible; adequate treatment should be commended.

Full history, biopsy, histopathological and immunological investigations are indicated.

Biopsy of the perilesional tissue is essential to the diagnosis.
Clinical skin diagnosis

- **Nikolsky sign**: firm sliding pressure with a finger separates normal-appearing epidermis, producing an erosion.

- **Asboe-Hansen sign**: Lateral pressure on the edge of a blister can spread the blister into clinically unaffected skin.
Pemphigus Vulgaris
Pemphigus blisters on the skin
Pemphigus on the skin

Most of Pemphigus patients have oral lesions:
Bulgarian (66%),
Italian (88%)
Israeli (92%)

Blisters is rather rare on the oral mucous surface erosion is visible without inflammatory courtyard.
Skin lesions
Primary skin blister

Secondary erosion on the skin
Tzanck cells

Prognostic sign to measure the level of Dsg1 and Dsg3

DIF HE
Pemphigus foliaceus is predominantly a skin disease.

- Oral or other mucous membrane involvements are very rare.
- Autoantibodies in pemphigus foliaceus, exclusively target desmoglein-1,
- In skin, desmoglein-3 is present predominantly in the lower layers of epithelial cells.
- Desmoglein-3 are present throughout the upper and lower layers of epithelium in the oral mucous membrane.
- Upper layers of epithelium of oral mucosa, is protected by desmoglein-3.
Paraneoplastic Pemphigus associated with lymphoproliferative diseases or cancer
In paraneoplastic pemphigus,

- Oral lesions can precede, follow, or appear at the same time of neoplasm discovery.
- Severe mucositis with hemorrhagic blisters, erosion, or ulceration.
- Lesions at the vermilion border almost always are present,
- the hemorrhagic stomatitis is extremely painful.
Therapy

SYSTEMIC TREATMENT,

CORTICOSTEROID
is the mainstay therapy for patients with oral lesions, transforming a fatal disease into one whose mortality is now below 10%.

The steroid level could be decreased until the patients are symptomless.
Steroid sparing materials

Azathioprin, chlorambucil, cyclophosphamide can be effective as adjuvant to steroid.

Methotrexate in low dose may be benefit.

There are studies with gold, prostaglandins, minocycline but their effect is not really confirmed.
Oral Care

Systemic immunosuppressant are essential
Topical or intralesional corticosteroid for localized oral lesions with low titer circulating antibodies
The treatment also consists of improving oral hygiene minimizing irritations of the lesions.
Pemphigoid Group

THE TARGET IS ONE OF THE PROTEINS OF HEMIDESMOSOMES
Diseases in this group

- Bullous Pemphigoid
- Benigne Mucosal Pemphigoid
- Cicatrical Pemphigoid
- Herpes Gestationis
- Epidermolysis Bullosa Aquisita
These diseases are autoimmune, subepidermal, blistering, producing blisters in the epidermal-subepidermal border.

IgG and C3 can be seen by direct immunofluorescence in the basement membrane zone.
Bullous Pemphigoid (BP)

It is a rare relatively benign autoimmune disease of the elderly.

There is no racial or gender prevalence. Most cases occur over 60, although cases have been reported in childhood too.
Pathogenesis

Bullous Pemphigoid is mediated by autoantibodies against hemidesmosomes of epidermal basal cells:

**Bullous Pemphigoid Antigen 230 (BPAG230)** cytoplasmic component

**Bullous Pemphigoid Antigen 180 (BPAG180)** transmembrane glycoprotein component

**Result:**
Dermo-epidermal separation
24% all of the cases have oral symptoms
Skin Manifestation

In the oral cavity due to proteolytic enzymes the blisters rupture within a short period of time.

In 7% of the patients the genital region is also affected.

Blisters are 1-7 cm in diameter their wall is thicker than in Pemphigus, better structured and much quicker heal than Pemphigus blisters.
Course and Prognosis

The mortality rate at 1 year was 19 in PV circulating autoantibody in BP patients who died in the first year of treatment,

- had high doses of corticosteroid
- low level of serum albumin.

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<thead>
<tr>
<th>Table 1-2 Pemphigus Vulgaris vs. Mucous Membrane Pemphigoid</th>
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<tr>
<td><strong>PEMPHIGUS</strong></td>
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<td>Target protein(s)</td>
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*Ig, Immunoglobulin; C, complement; BP, bullous pemphigoid antigen.*
Peripheral blood eosinophilia occurs in 50% of the patients. Elevated serum IgE level in 85%.

Remission of BP is paralleled by a decrease of serum IgE level.

different IgG subclasses reactive with BP180.

biopsy features in blistering disease:

the level of cleft formation intraepidermal or subepidermal

and the presence or absence of inflammatory infiltrate (eosinophil or neutrophil)

Histologically in BP there are subepidermal bullae with eosinophils in the dermis and bullae cavities.
Eosinophil cells in the blister
cleft

DIF has a high diagnostic value. In the basal membrane zone IgG, C3, IgM and sometimes IgA can be shown.
The degree of involvement and the rate of disease progression dictate the treatment.

Itching is controlled with hydroxizin (Atrax tabl.).

Systemic corticosteroid combined with immunosuppressive agents (azathyoprine, cyclophosphamide, metotrexat) have been the mainstay of therapy.
Benigne Mucosal Pemphigoid (Cicatrical Pemphigoid)

It is a rare subepidermal blistering and scaring disease characterized by autoantibodies against BMZ antigens (lamina lucida proteins involved in human keratinocyte adhesion to extracellular matrix).

The disease affects persons older than 40 years of age. The F/M ratio is 2:1. It is frequent on the eyes.
Oral mucosa are involved in 85% of the cases
Benign Mucosal Pemphigoid
(Cicatrical Pemphigoid)
Occular and Skin lesions

Out of 65% all the cases. The conjunctiva fibrosis then erosions leads to opacificatio and blindness.

Skin lesions:

25% out of the cases on the face, neck and hairy scalp.

The bulla erupted and heal with atrophic scar.
Opthalmological problems
Diagnosis

The biopsy shows a subepidermal cleft formation with little inflammation.

Direct immunfluorescence DIF of lesional, perilesional and normal mucous membrane shows linear deposition of complement and IgG less often IgA.
Therapy

Aggressively of the treatment depends on the severity of disease.

Oral, eye, genital, esophageal diseases needs aggressive treatment.

In the oral cavity intralesional corticosteroid, lidocain, Susp. Anaesth.

Systematically 0.5-1.0g corticosteroid daily.

Sometimes: Doxycyclin.
Erythema multiforme

It is one of the most common oral diseases

Most of the dentists can meet them in his practice

24-48 hours after allergen exposition develop the clinical signs

The autumn/spring incidence is the most common but it can develop any time
Erythema multiforme (EM)

• is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type III - IV hypersensitivity reaction

• associated with certain infections, medications, and other various triggers
In early stage IgM later IgG containing immunocomplex (IC) produced. Complement system activated on alternative pathway. The IC block the capillary vessel loops. The C3a and C5a complement factors play role as ANAPHILATOXIN which can release histamine from mast cells and basophile granulocytes.
- **Erythema multiforme minor** was applied to patients with the illness originally described by Ferdinand von Hebra as erythema multiforme (acute, self-limited condition with characteristic red papular skin lesions) (1860).

- **Erythema multiforme major** was applied to patients who also displayed oral mucosal involvement, similar to that described by Stevens and Johnson (mucocutaneous disorder; febrile erosive stomatitis, severe conjunctivitis, and disseminated cutaneous eruption) (1922).
Erythema (redness) multiforme (EM) is usually a reaction of the skin and mucous membranes that occurs suddenly.

It appears as a rash on skin and may include mucous membrane lesions.
The clinical symptoms develop 24-48 hours after antigen exposition. Frequency increase in spring and autumn but it can develop in every time. After 6-8 recurrences a longer interruption follow, and then begin again.
Classification

- Erythema multiforme caused by a reaction to medication, type III immune reaction
- or a type IV hypersensitivity reaction to an infection (caused most often by Herpes simplex) and it is relatively benign
- Stevens–Johnson syndrome (SJS) is a milder form of ..... 
- Toxic epidermal necrolysis (TEN).
- These conditions were first recognised in 1922
- Both diseases can be mistaken for erythema multiforme.
Clinical characteristics

- **Erythema multiforme** is an acute condition which can spontaneously heal but may require treatment for the symptoms.

- **Erythema multiforme minor** - Typical targets or raised, edematous papules distributed acrally.

- **Erythema multiforme major** - Typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes; epidermal detachment involves less than 10% of total body surface area (TBSA).

- **SJS/TEN** - Widespread blisters predominant on the trunk and face, presenting with erythematous or pruritic macules and one or more mucous membrane erosions;

  - epidermal detachment is less than 10% for Steven-Johnson syndrome and 30% or more for toxic epidermal necrolysis.
Recent classification

- Stevens-Johnson syndrome was separated from the erythema multiforme.
- Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) are considered severity variants of a single entity.
  - (1) erythema multiforme consisting of erythema minor and major.
  - (2) Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN).
Clinical characteristics

- Erythema multiforme is an acute condition which will usually go away on its own but may require treatment for the symptoms.

- **Erythema multiforme minor**
  - Typical targets or raised, edematous papules distributed acrally

- **Erythema multiforme major**
  - Typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes; epidermal detachment involves less than 10% of total body surface area (TBSA).
Steven-Johnson syndrome
In the German literature Epidermolysis Plurioroficialis.

Large blisters can be found not only in the oral cavity, but on the skin.
common mild form is refer to as EM minor.

- skin rash that involves no more than one mucosal surface.
- classic iris or target lesions.
- They have bright red borders and small white bumps in the center.
- The causes:
  - viral
  - chemical products,
  - antibiotics - specifically penicillin or cephalosporin.
Erythema multiforme minor

- a localized eruption of the skin with minimal or no mucosal involvement.
- The papules evolve into pathognomonic target lesions or iris lesions within a 72-hour period.
- Lesions remain in a fixed location for at least 7 days and then begin to heal.
(HSV)–associated erythema multiforme

- this is now recognized as a variant of erythema multiforme, rather than Steven-Johnson syndrome.

- Erythema multiforme with mucosal involvement is now termed bullous erythema multiforme.
Erythema multiforme minor

- **Precipitating factors:**
  - herpes simplex virus (HSV),
  - Epstein-Barr virus (EBV),
  - histoplasmosis.

- **persistent antigenic stimulus - recurrence is common**

- **affected individuals experiencing 1-2 recurrences per year.**
Erythema multiforme major

- More severe, potentially life-threatening disorder
- Most patients have extensive mucosal involvement.
- More than 50% of all cases are attributed to medications.
Postherpetic Erythema Exudativum Multiforme

Minor form:

In these cases the HSV play role not only infective agent, but as antigen too.
Stevens–Johnson Syndrome

- is named for Albert Mason Stevens and Frank Chambliss Johnson,
- Two American pediatricians who jointly published a description of the disorder in the American Journal of Diseases of Children in 1922
Stevens–Johnson syndrome (SJS)

- Usually begins with fever, sore throat, and fatigue,

- Bulla, erosions and ulcers appear in the mucous membranes, in the mouth, lips, genital and anal regions.

- In the mouth usually extremely painful and reduce the patient's ability to eat or drink.

- Conjunctivitis occurs in about 30% of children who develop SJS.

- A rash of round lesions about 3cm across arises on the face, trunk, arms and legs,
Stevens–Johnson syndrome (SJS)

- A rash of round lesions about 3cm across arise on the face, trunk, arms and legs,

- Bulla, erosions and ulcers appear in the mucous membranes, in the mouth, lips, genital and anal regions.
clinical definitions of erythema multiforme and Steven-Johnson syndrome

• whether they are distinct entities or whether they represent a spectrum of one disease process?

  erythema multiforme and Steven-Johnson syndrome could be separated as 2 distinct clinical disorders

• with similar mucosal reactions but different patterns of cutaneous lesions.
Therapy

- Anti-histamines systemically:
  - Inj. Calcimusc i.v., Tab. Zyrtec, Caradonell,
  - Caps. Fenistil
  - Corticosteroid ??? (frequent recurrences)

- Anti-infective oral rinsing:
  - Chlorhexidine
  - Betadine
  - Listerine
If the patient needs painkiller
Susp. Anaesth.
Tabl. Cataflam
Tabl. Rubofen
Tabl. Diclophenac

Never give amidasophen and novamidasophen containing drugs!!!!!!