**Behcets Syndrome**

We have to make sure that aphthous ulcer forany patient is part of behcets syndrome or not.

**Etiology:** unknown

Immune mediated.

Patients with HLA-B51 (antigen) would be more susceptible to be infected with behcets syndrome.

Usually adult males

Usually clinical diagnosis,

Inflammation affected eyes

**Major criteria:** (asking about behcets syndrome we have to ask about these symptoms)

1- aphtous ulcers (oral), greater number, mostly concentrated in the oropharynx, variable in size, could be irregular borders, large zone of erythema (redness around the ulcers is more than around normal aphthous ulcers).

2- eye (uveitis inflammation, conjunctivitis, retinitis)- so any part of the eye could be affected

3- genital ulcers (apthous-like ulcers in the genital areas)

other minor things that affect skin (papulae and pustular eruptions- acne-like lesions, erythemal nodosum-itchy red nodules ), vein inflammation, subcutaneous thrombophlebitis, joints, GIT and CNS.

A test could be done to patients with behcets disease to confirm diagnosis; minor stick using a needle (Skin Prick Test) will lead to nodules, redness followed by mastule in the area. The immune system gets more stimulated in these people, because behcets syndrome is immunedeated that leads to vasculitis all over the body .

 So, a positive pathergy test is a major component that confirms the diagnosis of behcets disease.

**Minor criteria:**

1-pain in joints (arthralgia).

2- CNS lesions (depression,…)

3- thrombotic vascular lesions

4- GIT lesions ( ulcers)

So, it's mainly clinical diagnosis and we have to look for major and minor criteria.

Vesiculobullous disorders is another type of ulcers. Vesicles appear first, then bullae that rupture (secondary not primary ulcers- same as viral infections).

A group of diseases (infections, autoimmune, hereditary diseases).

Vesicles of bullae>rupture>ulcers

*Whats the difference between vesicles and bullae?*

*size (bullous are larger than vesicles)*

Vesiculobullous disorders are also divided according to the area of the vesicle or the bullae.

If it were in the epithelium, similar to viral infections, it's called intraepithelial lesions. Pemphigus vulgaris is an autoimmune, intraepithelial lesion. Follicular keratosis, genetic, white lesion is also considered a vesicullobullous disorder and non-acantholetic viral infections.

(acontheletic: loss of the contact between the epithelial cells-loss of desmosomes, so in that area vesicles will form or cavities within epithelial cells that lost connection with fluid).

In viral infections what caused vesicles in the epithelium was damage (rupture) to the epithelial cells (non-acantholetic).

Intraepithelial vesicles contain clear fluid because there is no blood within the epithelium.

There are a group of diseases that cause subepithelial vesicles of bullae( full thickness of epithelium above the cavity) such as Bullous lichen planus, Erythema multiform, Epidermolysis bullosa, Dermatitis herpitiformes, Linear IGA disease, Oral blood blisters and Pemphigoid.

In hisopathology the area of the vesicles (clefting, space) is beneath the full the thickness of the epithelium (the area of loss of contact is below the basement membrane or within it).

**Pemphigus vulgaris:** the most dangerous

 **Pathogenesis:**

It's an autoimmune disease, antibody mediated (auto antibodies against certain antigens). These antigens that exist the skin and mucous membranes are part of the desmosomes (protein desmologen 3)

So, pemphigus leads to desmosome damage, that's why the area of vesicles will be within the epithelium (intraepithelial).

It can affect the skin leading to loss of superficial parts of it leading to vesicles, then these veicles rupture easily because they aren't thick. Loss of skin will lead to the loss of fluids, minerals,….etc. The patient may also be exposed to infections which could lead to death, that's why it was a very severe disease before the corticosteroids discovery.

While the pemphigoid is autoantibodies against components of the basement membrane or hemidesmosomes connecting basal cells with the BM.

 **Clinically:**

Uncommon disease

Mainly females

Middle aged patients (40-60 years)

50% oral lesions could be the initial site, while if skin was affected first the oral cavity will be affected later.

In a minor percentage of patients it could only be found in the oral cavity.

The roof of vesicles are thin because they are intraepithelial (fragile) ,compared with the pemphigoid, painful, erythematous erosions.

Borders are the remnants of the epithelium, that's why you find it of irregular borders and there are parts of epithelium detached from the underlying tissue surrounding it.

Most areas affected are areas with trauma ( lateral border of the tongue, buccal mucosa, vesicle occlusal line, areas that are exposed to mastication)

Pemphigus vulgaris can affect other sites such as nasopharynx,eosophigus, vagina...etc.

Nikolsky's sign is to prove your diagnosis, (finger pressure on a specific area will lead to detachment of the epithelial cells from each other leading to the formation of vesicles or bullae at that site, and if you press on a vesicle or a bullae this will lead to a lateral spread) is positive in pemphigus vulgaris.

**Histologically:**

Clefting is within the epithelium above the basal layer.

The basal layer stays attached to the basement membrane, it's within the prickle cell layer above the basal layer, "tombstones".

Mild inflammation in the lamina propria, the cell mediated immunity isn't responsible as in the aphthous ulcer.

In this case we notice the autoantibodies in the area of desmosomes, so it doesn't rely on the cell mediated immunity, they only appear in reaction to the process.

Tzanck cells ( shrinked cells –epithelial cells after they lost their connection together- could be found within the vesicles or if we did aspiration in the area of the vesicles and put it on a glass slide you'll notice their existence), could be part of diagnosis.

While if it was herpes infection, tzanck cells wouldn't exist, there would be rupture in the cells all around and giant cells would appear.

To confirm that the cause is autoantibodies we us the direct immunofluorescence test, another antibody carrying a fluorescence dye against the IGg antibody in the area of desmosomes, therefore it will indicate the site/existance of the autoantibodies.

We usually take the biopsy from the area surrounding (alongside) the ulcer, beacause they could exist in different concentrations within the ulcer, to ensure that there is greater concentration of the autoantibodies and they exist in the same concentration in the area around.

It's not put in formalin.

The process of the direct immunofluorescence:

frozen with liquid nitrogen, or if you were at the hospital with formalin quickly with a gauze to the immunology lab "not the pathology lab", and they would do the test at the lab after you fill in a form of what test you want to do

Positive: border of cells appear clear with dye

It's a fishnet appearance or a chicken wire.

Indirect imunofluorescence is also positive in these patients; it's taken from the serum of the patient, put on a tissue ( animal tissue, eosophigus,….), then autoantibodies that contain fluorescent dye are added.

So, it measures how much antibodies are in the serum innervation. As the concentration rises the severity of the disease is more.

If you want to do monitoring to know if a disease is severe or not you can depend on the level of the autoantibodies that exist in the serum.

Other forms of pemphigus disease are :

**Foliaceous**; antibodies exist in the superficial parts (above the prickle and below the parakeratin layer), that's you'll notice the area were detachment occurred is a superficial part of the epithelium. So, it's severity is less than the pemphigus vulgaris.

A type that occurs after ulcerations is called "V**egetans**", growth and granulation tissue which is a very rare type.

A type associated with neoplasm, it could be benign or malignant tumors is called "**Paraneoplastic pemphigus**".

If we knew that the patient has this tumor and ulcers we would expect it to be pemphigus.

***What is the pathogenesis "what is the relation between both –autoimmune and a tumor-"?***

**Pemphigoid**

Erosions in the oral cavity

Racked borders

While the aphthous ulcer is of localized ulceration, well-defined, of a certain number, localized lesions.

It's a deeper location to the split or clefting.(below the full thickness of the epithelium, the area of the basement membrane).

It's an autoimmune disease.

IGg and C3 exist in the basement membarane ; if we do the DIF you'll notice linear deposits in the area of the basement membrane.

*Is it only pemphigoid that we get to think about seeing the linear deposit in the BM?*

*No, Linear IgA disease. They differ in the type of the autoantibody; IgG in the pemphigoid while its an IgA in the Linear IgA disease.*

A protein exists in the BM called the bullous pemphigoid antigen 1, bullous pemphigoid antigen 2. these are the antigens which autoantibodies are against.

Indirect immunofluorescence isn't positive in all patients, only up to 80%. so we mainly depend in the diagnosis on the DIF.

**Histological:**

Starts at the basement membrane in the shape of focal edema. you don't find local inflammation from the beginning because it's not caused by cell mediated immunity.

Then separation of the full thickness of the epithelium in the area of lamina lucida.

In the full developed lesion vesicles will exist or cavities or spaces that contain fluid under the full thickness of epithelium.

Perivascular inflammation of the lamina propria.

Inside the vesicle you could also notice inflammatory cells from the lamina propria.

Rupture could occur to these vesicles, and because they exist below the epithelium were there are blood vessels, therefore the content would be blood instead of clear fluid.

Because of it's full thickness (roof), it lasts for a longer time in the oral cavity.

If rupture occurred the ulcer would be deeper. longer time to heel.

And because it's subepithelial it could lead to scarring after treatment.

It's called "hemorrhagic bullae" .

Patients with pemphigoid are elder (70-80 yrs) than patients with pemphigus (middle aged).

Females>Males

Less severe than the pemphigus although it's deeper, but it's distribution in the body is less.

Pemphigus is all over the skin, mucous membranes, it's difficult to control and needs high doses of the cortisone while the pemphigoid is localized to certain areas.

**2 types:**

**1- Bullous Pemphigoid**

Affects the skin, rarely the oral cavity (only in 10%).

Diagnosed with direct immunofluorescence and 75% of cases of Indirect immunofluorescence are positive.

**2- Mucous membrane pemphigoid**

Affects mucous membranes including the oral cavity.

The skin is rarely or isn't affected at all.

In the oral cavity it usually precedes the other sites.

In some patients the oral cavity could be the only site (localized), it could be even localized to certain sites in the oral cavity.

The bullae is a tense (not flaccid), compressed because it's roof is strong and can bear higher pressure.

While the pemphigus is usually flaccid, not totally blown, because rupture would occur.

Tough (greater thickness)

It stays in the oral cavity for a few days while in the pemphigus you'de rarely see a patient with an intraoral vesicle that has turned to ulcers ( as soon as the vesicle forms it ruptures directly).

When rupture occurs this will lead to erythematous areas, well-defined margins because they are deeper.

Slowly heels, could take a few weeks, and scarring could occur afterwards.That's why it's called "Cicatricial pemphigoid".

It's sometimes localized to one area, and the gingiva could be the only affected site.

In the gingiva it's usually desquamatous gingivitis (clinical term for certain diseases; lichen, pemphigus or pemphigoid).

So, one of the things that characterizes pemphigoid that even if the patient has other vesicles in the oral cavity, the gingiva could be affected with desquamation.

The only manifestation could only be this appearance, were the full thickness is affected.

Scarring to the conjunctiva or adhesions (symblepharon) could lead to blindness.

Other affected areas such as the nasopharynx, larynx esophagus and genital areas.

**Erythema Multiforme:**

Erythema:redness

Multiforme:different shapes

**Clinically:**

Affects younger aged adult groups

Males> Females

Abrupt onset

Some patients with a prodromal phase; nonspecific signs and symptoms "lymphadenopathy, fever, cough, pharyngitis", then after that he gets the erythema multiforme.

Could affect the oral cavity alone, the skin alone or the oral cavity and the skin together.

vesicles, bullae that rupture leading to erosions and redness in sites in the oral cavity or on the lips.

It's mainly a clinical diagnosis, with no test used to confirm it. because even if we took a biopsy there wouldn't be any specific features (it could be intraepithelial or subepithelial), and there isn't any positive DIF.

What distinguishes it from others is that it's a clinical diagnosis that depends on certain features such as skin lesions, if they exist "target" or "iris" lesions are concentric layers of erythema and edema .

In the center you could find vesicles or ulcers "ulcer vesicles" or red area surrounded by circles are on the hands or feet and could help in diagnosis/.

**Oral lesions:**

Especially the lips and anterior mouth you'll notice erythematous, vesiclobullae that have ruptured and led to erosions and ulcers, are all nonspecific features.

Crusting to the lesions could occur "circumoral crusting".

So, when seeing "circumoral crusting" you'll think of two cases; erythema multiforme and herpes.

They remain 10-14 days (2 weeks) then healing occurs.

Recurrent lesions.

In severe forms "stevens-johnson syndrome";

White spread involvement of the skin and the mucous membranes, and the patient should be hospitalized and given an antibiotic, analgesic, cortison.....etc, to stable the condition.

The **pathogenesis** is unknown, but it's connected with predisposing factors which are:

1-Herpes; were the patient was infected with herpes virus "herpes labialis" before the erythema multiforme. (mild form)

2- Certain drugs; sulphonamides (severe form)

So, if a young adult with a lot of erosions, crusting on the lips, you have to ask him in this case about history of herpes.

They relate these with herpes that the antigen against it in the immunity is the herpes virus.

antigen; herpes virus....autoantibodies created against it.......antigen-antibody complex.....deposition in the blood vessels which lead to inflammation in some areas.

Or if it were in the severe form the antigen would be the drug itself.

**Type 3 hypersensitivity:**

Antigen-antibody complexes or autoimmune disease

Deposition of immunocomplexes which is IgM and C3 in superficial vessels....inflammation to the blood vessels...ischemia will occur in the areas that are fed by these blood vessels....ulcerations and erosions.

**Histopathology:**

Taking a biopsy only will show that this disease causes vesicles or bullae.

Necrosis to the surface epithelium "necroticlid" due to ischemia.

Chronic inflammatory cell infiltrate in the lamina propria.

**Dermatitis Herpitiformes:**

Dermatitis; skin

Herpetiformis; close to the herpes.

Rare skin disorder.

Rich, itchy rashes mostly on the shoulders. other parts of the skin may also be infected.

They relate Dermatitis Herpetiformis to the celiac disease; so it's a skin manifestation of the celiac disease.

These patients also have GIT disease (gluten hypersensitivity; they can't eat any food related to wheat).

Oral lesions are non-specific; red areas, erythematous areas, vesicles, bullae, erosions.

Could affect the palate, buccal mucosa.

*How to confirm diagnosis?*

*Granular deposits of IgA and C3 noticed when doing the direct immunofluorescence test on the tip of the connective tissue papillae (so, it's a focal deposition not linear).*

**Histology:**

Microabscesses on the tips of the connective tissue papillae.

It's non-continuous (focal, microabscesses).

**Linear IgA disease:**

The difference between it and the dermatitis herpetiformis is that it's linear instead of being focal.

It's not associated with the ciliate disease.

It could be associated with internal malignancies such as lymphoma.

**Epidermolysis Bullosa:**

30 types or more.

Mostly genetic, therefore family history and vesiculobullous disease.

Other vesiculobullous diseases are immune mediated.

**Types:**

1- Intraepithelial

2- Subepithelial

Every time the patient is exposed to trauma, vesicle bullae will be in that area then they will rupture and scars ill occur because it's mostly subepithelial.

Deformities will also occur.

Sometimes it's severe that during birth loss of the skin occurs , the baby dies.

But if it were milder forms he lives but with deformities ( areas with ulcers and scarring. therefore, deformities in the areas he uses a lot; knees elbows, face).

Early life helps in diagnosis .

Bullae in areas of cytopressure then contracture in the area (as you notice in the picture were there's contracture to the fingers and the hand is full of scarring).

**Oral cavity:**

1- limitation of mouth opening.

2- trismus.

3- decrease in tongue mobility (poor oral hygiene).

4- difficult access for the dental treatment of oral hygiene.

 5-any intraoral treatment can cause vesicles or bullae and erosions.

6- it affects young patients causing enamel hypoplasia.

**Oral blood blisters**

 Large vesicle or bullae localized **only** in the palate; it grows until it ruptures, then it heals.it could recur once again.

Doesn't affect the skin

Spontaneous blood filled (subepihelial) bullae.

It's mainly 1 bullous.

2-3 cm in diameter then it ruptures and an ulcer forms.

The patient may feel suffocation because it affects the posterior part of the palate. and that's why it's sometimes called "angina bullosa haemorrhagica".

The patients that get infected use inhalers (cortisone)- asthmatic patients; the cortisone affects the collagen, so the collagen synthesis and strength gets weaker in this area and splitting occurs in the subepithelial area.

**Immunological finding:**

 negative DIF test.

|  |  |
| --- | --- |
| PEMPHIGOID | PEMPHIGUS |
| below the full thickness of the epithelium, the area of the basement membrane). | within the epithelium (intraepithelial) |
|  against hemidesmosomes connecting the basal cells with the basement membarane | within the epithelium (intraepithelial) |
|  old patients (70-80 years) | middle aged patients (40-60 years) |
| clefting is below the full thickness of the epithelium, the area of the basement membrane,. | Clefting is within the epithelium above the basal layer |
| painful, erythematous erosions. | The roof of vesicles are thin because they are intraepithelial (fragile)  |
| autoantibodies | autoantibodies |
| DIF, IDIF | DIF,IDIM |
| linear appearance | fishnet pattern, chicken wire appearance |
| IgG and C3 | IgG |
| the bullae is tense | the bullae is flaccid |
| Blood within the vesicles | clear fluid within the vesicles |
| Localized areas | All over the skin and mucous membranes |
| less severe | more severe |