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PEMPHIGUS *

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Definition

Pemphigus is a bullous dermatosis of unknown etiology whose histological feature is a acantholysis usually with severe evolution.

Etiopathogeny

Since the 60's a description of the presence of autoantibodies against the epithelium has existed. These produce changes in the intercellular cement and in the desmossomes (intercellular union substance) followed by formation of intra epidermic loss. The autoimmune mechanism might well be responsible for this, although a definite causing agent has not been detected.

Classification

In accordance with clinical appearance and the hystopathology of the bullae, the pemphigus can be diveded into two main clinical manifestations:

I) Pemphigus foliaceus II) Pemphigus vulgaris

I) Pemphigus foliaceus

Epidemiology

It is a world wide disease which is endemic in many Brazilian states, in particular Goiás, Minas Gerais, São Paulo, Distrito Federal, Paraná and Mato Grosso do Sul. In areas where the disease had not previously existed, cases are now being registered much more frequently. This is so in São Paulo, Paraná and Minas Gerais. Indeed, over the last few decades, the prevalence of the disease has increa-

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sed significantly in the central area of Brazil. *Pemphigus foliaceus* is also endemic in neighbouring countries such as Paraguay, Peru and the Northern Argentina.

Until July, 1989, 4.998 cases had been registered in the OSEGO Tropical Disease Hospital in Goiania, with an average of 10 new cases been reported per month in recent years.

The *Pemphigus foliaceus* is characteristic of rural areas, being rare in metropolitan areas. There are family cases registered, but the avaiable data do not suggest interhuman transmission, rather the people of the same family are living together in an endemic source.

Age group

The highest incidence of cases occurs amongest young people between the ages of 15 and 30 years old, althought it may also occurs in children and older people. However the number is far fewer.

Clinical manifestation

It manifests with different aspects according to the stage, having the following forms.

a) abortive
b) bullae exfoliative or "invasive"
c) chronical erytradermic

No mucosal lesions are observed in any of these stages.

a) Abortive form

This manifestation is characteristic of the early phase of the disease, with few lesions often located on the scalp, face and upperchest, with clear preference for the seborrheic areas (*Seborrheic pemphigus*). In some cases, the erythematosus lesions on the face, with a "butterfly" distribution, are reminiscent of the *Lupus erythematosus* (Pemphigus erythemathosus).

The lesions have an erythemathosus, scaly or oozy aspect, and bullae are rarely observed.

Once the clinical picture of the abortive stage is set, the lesions can recede either gradually or spontanleously leaving erythemato-hypochronic or hyperpigmental stains. On the other hand, they might recede and be substituted by new lesions, keeping their benign character. At this stage, pruritus can occur in the lesion. Apart from this, no significant general changes are observed.

In some cases a sudden spreading of the lesions progressing into another clinical stage, that "of invasion", is observed.

The evolution of the Abortive Form is unforeseem.

The Nikolsky sign may be present in the proximity of the lesions.

b) Bullae Exfoliative or "invasive"

The phase of invation can occur immediately after the early lesions have appeared of after variable time, but

the great majority of pemphigus become Bullae Exfoliative in the first weeks or months.

In spite of the time spent between the Abortive and Bullae Exfoliative stages, the features will always be the same: metameric and symmetric distribution of the bullae, often descendant, being of variable dimensions (They can reach many centimeters). The bullae are flacid and break easily leaving an extensive denuded erythemathosus and oozy areas. The following phase is the scalyerythemathosus phase with great scale elimination.

Nikolsky sign is always present, preceding in the region that will next be attacked. The lenght of time of this "invasion" phase is relatively short that is, extending over a few weeks.

In this phase, the signs and symptoms are those of an acute infectious disease: That is evening time fever, malaise, headache, shivering, weakness, extreme sensitivy to cold, anorexia and weight loss.

The faster the invasion, the more intense the clinical picture. In rare cases, the patient can die without ever reaching the chronic stage.

Pemphigus foliaceus is also known by the name of "wild fire" because of the look of the lesions and the burning, raging felling in the skin.

c) Chronic erythrodermic form

As the disease progresses, the blisters become less evident being substitute by erythema and a less foliaceus scaly but more scurfy surface, that can compromise the cutaneous level.

This phase extends over many years, and different clinical varieties can be found: some patients present an oozy erythemato-pigmentary lesions that can become confluent. Other patient present an oozy, scaly, red skin as if covered by a "humid mass". These patients are the ones in which the disease takes more time to reduce.

The papillomatous variety is the most rare form and has one curious feature: The dermic papillous becomes protusive, rising up 0,5 to 1 millimetres above the level of the skin, remaining separate and not coalescing. They are very reminiscent of the granular skin of the blackberry in appearance.

Changes in annexus the Chronic Erythrodermic phase are observed. There are loss of hair, eyelash, axillae and pubic hair and nail distrofied. There is a scaly seborrheic scalp and keratosis "palmaris et plantaris".

At this stage of the disease, there is a progressive loss of weight leading to cachexy and weakness. The patient becomes bed-ridden, suffers ankylosys, bone decalcification, pathological fractures, and has low resistance to intercurrent infections and often death.

In spite of the severe clinical picture, if the patient is kept free of complications and receives adequate medical care, the disease recedes gradually and pigmentary stains appear in the areas previous attacked.

Children or young patients affected by *Pemphigus foliaceus* present delay or even interruption in physical and menthal development.

II) Pemphigus vulgaris

It is the most uncommon form, but it is worldwide. It attacks both sex, and it is more common in the post 40 age group, presenting a more severe prognoses, progressing, not rarely, into death.

Clinics and diagnoses

The blisters appear on the skin and/or in mucoses, are tighter than in *Pemphigus foliaceus*, with a clear or dark or even hemorrhagic content. The mucosal lesion can precede the cutaneous blisters for a long time, making difficult the clinical diagnosis, generally labelled as "chronic stomatitis".

Pemphigus vulgaris has a clinical variant called *Pemphigus vegetans*, where the broken blisters are succecded by vegetant lesions with centrifugal expansion.

Both in *Pemphigus vulgaris* and in its clinical variant, lesions are more likely to attack the mucoses and cutaneous folds, although they can progress into another areas, aggravating the general clinical picture of the patient.

Associated Pathologies

Given the nature of the disease and/or the use of corticosteroids, the patient requires careful attendance. This is necessary to prevent the subsequent infections and it should always be borne in mind that the use of corticosteroids can mask or reduce the signs or symptoms of some of these manifestations.

Infections

Reappearance of pulmonary tuberculosis, bronchiopneumonia, pyodermitis, urinary infection, superficial mycosis, viruses. The superposition of certain factors facilitates the onset of infections. They are: general state of debilitation, extensive areas with continuty solution on the skin, immunosupression caused by corticostherapy.

Infestations

The patients showd be routinely evaluated before the cortisonic therapeutics is instituted.

Other pathologies

Peptic ulcer, pancreatite, arterial hypertension, Cushing Symdrome, psychopathies.

Differential diagnosis

Difficulties of diagnosis will be similar to those of other bullous diseases.

Dermatites herpertiformis

Also known by the name of Durhing-Brocq or painful poliforms. The blisters are thicker, there are polymorphic lesions (bullae, vesicles, urticary erythema). The lesions have a liquid content, they tend to amass and are reminiscent of the herpetic lesions. This form of dermatitis can be accompanied by disabsortive symdrome and patients feel pain or prurid in the lesions.

Polymorphus erythema

There are also polymorphic lesions, erythema or liquid content lesions that are arranged in concentric circles (Iris erythema or Iris herpes). The blisters are subepidermic.

Lyell Symdrome: (Toxic epidermic necrolisis)

Acute manifestations, often lethal, caused by allergic reaction to staphyloccocus or drugs.

The epiderm becomes dark and detaches in large pieces. The Nikolsky sign should be carefully applied since skin dislodgement will occur in areas already identified as being clinically alterated.

Impetigo

Sometimes it is difficult to diagnose Impetigo when it manifests through spread lesions. The blister of Impetigo is located immediately under the corneal layer. The features are similar to those of pemphigus. The diagnosis of Impetigo can be suggested by the epidemiological data, lesions being located in juxtaposed skin folds (by autoinnoculation) and the absence of the Nikolsky sign.

Pemphigoids

Pemphigoids is a rare disease which mainly attacks children and old people, where it can manifest as a hidden neoplasic disease. The blisters are large, thick and do not burst easily.

Epidermolysis bullosa

It is a dermatose related to the genes caused by dominant or recessive autossomal inheritance that appears immeadiately after birth or in early childhood. It is rarely found later. The blisters appear in areas of traumatism.

Familiar begnin chronic pemphigus: (Hailey-Hailey)

It is transmitted by dominant autossomal inheritance. The blisters appear on limited areas of the body which are in general otherwise healthy. There is a tendency to select the folds of the skin. They can form denuded areas with polycycle autlines. Although acantholic blistering is present as in pemphigus, the histopathological exam is characteristic.

Lupus erythemathosus

The diagnostic differential should be done with the abortive form

of *Pemphigus foliaceus* that may present lesions in a "butherfly wing" distribution.

In pemphigus an intensive scaling of the scalp is observed as well as bullae lesions in other areas of the tegument. When the bullae appear in the lupus erythemathosus, a lupus systematization has probably occured. This can be checked by laboratory exams (Le cells, ANF). In abortive pemphigus lesions, a crust scaly is observed and in lupus erythemathosus the lesions are keratosic, dry and adherent.

Complementary Exams

Biopsy: A recent whole blister must be removed. The material must be fixed in 10% formol. The histopathological exam is the most utilized and it is very characteristic of the disease.

In histology, the characteristic pemphigus alteration is the presence of the intraepidermic blister, produced by acantholysis. Inside the blister, large, isolated cells can be observed. These are the acantholysis cells.

There is a histopathological difference between *Pemphigus vulgaris* and *Pemphigus foliaceus*. In *Pemphigus vulgaris* the blister is above the basal layer, therefore, deeper and thicker. In Pemphigus foliaceus the blister is more superficial, that is under the granulated layer and as a consequence it breaks easily.

Citodiagnosis of Tzank: The material is obtained by scraping of the base of the blister. It is than fixed in methilic alcohol and stained with Giemsa or Leishman, which will show the acantholytic epithelial cells.

Immunofluorescence: This is not routinely carried out. both the direct and inderect immunofluorescence indicate the presence of Ig G class of intercellular antiepithelial antibodies in the different kinds of pemphigus.

In *Pemphigus foliaceus* the indirect immunofluorescence reveals elevated titers of these antibodies. Although there is no perfect clinico-immunological correlation in all cases, the antibodies titers seem to be related to the extension of the disease. In *Pemphigus vulgaris*, the indirect immunofluorescence reveals Ig G titers inferior to those in the *Pemphigus foliaceus*. However, in Pemphigus vulgaris the clinico-immunological correlation is precise and it is also useful for the terapeutic control.

TREATMENT

I) Pemphigus foliaceus

Corticoids are administrated in equivalent doses of 40 to 120 mg of prednisone per day, in a scheme that varies in accordance with each case.

In the OSEGO Tropical Disease Hospital in Goiânia, the prednisone is administrated to hospitalized patients with extensive lesions, in the following manner:

120 mg on the 1rst and 2nd day
100 mg on the 3rd and 4th day
80 mg on the 5th and 6th day
60 mg from the 7th to the 10th day
40 mg from the 11th to the 20th day
20 mg from the 21rst to the 30th day

As a general rule, this scheme should be respected, and some variations can occur according to the evolution. The patient will be hospitalized, on average, for 30 days. After the discharge, the patient should take a mainteinance dose of 5 to 10 mg of prednisone daily, and should return for a check-up visit every 3-6 months.

Some patients need to keep this dose for an indeterminante time, others have relaps that require hospital admittance. A third group progresses slowly to total control of the disease, demanding reduced maintenance doses each time until the drug is completely suspended.

Any kind of corticoid can be used and when it is possible to choose, triamcilona is used.

Antibiotics appropriated to the cultures and antibiogram are used in the event of secondary infection. Erythromicine, tetracycline or penicillin are currently used in pemphigus patients with domiciliary bacterian infection.

Tropical medication has little influence on the evolution of the disease although it may be recomended to enhance the patient's well-being. Therefore, baths with 1:40000 potassium permanganate solution are recommended in the case of oozy or bullae lesions, followed by the application of vaseline. An antibiotic ointment is used when there is a bacterian infection. A hyperproteic diet is prescribed to maintain the patient's general state, apart from nursing care.

In spite of the progress in corticotherapy *Pemphigus foliaceus* still has a reserved prognosis. Mortality has drastically reduced, oscillating between 5 and 10%. Interruption of the treatment is determinded by clinical criteria, although clinical manifestations predominate over the laboratory exams.

II) Pemphigus vulgaris

The treatment is identical to that for *Pemphigus foliaceus* although it requires greater initial doses (80 to 300 mg of prednisone daily) and greater maintenance doses. The prognosis is "sombre" and the smaller corticoid maintenance dose is, the better it will be.

The average life-expectancy of the cases treated is five years. The association of corticoids with immunosupressors, azatioprina, cyclosfosfamida and methotrexate has been useful. This association is particularly recommended in severe cases, because it allows a reduction in corticoid doses. Gold (gold sodium thiomalate or aurum tioglicose) has also been used in association with corticoids.

Despite the severe clinical picture and high mortality, no systemic attack is registered at necropsy. The

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findings of visceral and central nervous system alterations are interpreted as being the result of metabolic alterations which in turn are the result of the cutaneous and non-organic lesions of the disease itself.