Methodic elaboration for practical lesson in

Dermatovenerology

for students of Medicine Faculty nr.2

Topic N8

Pemphigus Dermatitis herpetiformis.
Ichthyosis vulgaris. Epidermolysis bullosa.

PEMPHIGUS

Pemphigus is severe and potentially life-threatening. There are two main types. The most common is pemphigus vulgaris, which accounts for at least three-quarters of all cases, and for most of the deaths. Pemphigus vegetans is a rare variant of pemphigus vulgaris. The other important type of pemphigus, superficial pemphigus, also has two variants: the generalized foliaceus type and localized erythematosus type.

Etiology

The nature of pemphigus as an autoimmune disease of the skin is now established. Numerous studies have confirmed the presence of serum autoantibodies reactive with antigen (s) lacated in the intercellular spaces between individual epidermal or mucosal cells. These intercellular substance (ICS) - reactive antibodies are of the IgG type, are demonstrable by indirect immunofluorescece (IF), and are found in all forms of pemphigus, an additional feature unifuing members of the pemphigus group. Autoantibodies are directed against a 30-kDa glycoprotein designated desmoglein 3'. Levels of ICS antibodies often fluctuate with disease activity' and, immunopathologically, they react precisely at sites of the primary pathologic process,t he ICS areas of the skin. Strong evidence now implicates these antibodies as the cause of acantholysis. By direct IF staining, both IgG and complement deposition occur in ICS areas of early pemphigus lesions.

PEMFUGUS VULGARIS

Cutaneous manifestations : Clinically, the characteristic feature of pemphigus vulgaris is the presence of flaccid, weeping bullous lesions which leave large, denuded areas of the skin. Lesions may arise on normal appearing skin. Because of their location within the epidermis, pemphigus blisters rupture easily; crusting may be the only clinical evidence of a bullous process. Most patients develop the mouth lesions first. Shearing stresses on normal skin can cause new erosions to form (a positive Nikolsky sign). Nicolsky,s sing, a dislodging of the epidermis with lateral finger pressure, is frequently present; especially in-patients with active, widespread lesions. The Asboe-Hansen sign (also known as "indirect Nikolsky sign" or "Nikolsky II sign") refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla. Cutaneous areas commonly involved include the scalp, umbilicus, and the intertriginous areas. The mucous membranes are commonly involved and are often the presenting symptomatology. Oral lesions may precede cutaneous lesions by several months, and unless the diagnosis of pemphigus is suspected, the condition is often misdiagnosed. Most of these patients carried a diagnosis of aphtous stomatitis for at least a year before the correct diagnosis was made. Oral lesions may be so extensive and painful as to interfere with the intake of solid food; lesions may involve pharynx and larynx, which may result in hoarseness. Involvement of the conjunctiva is not uncommon and may precede oral lesions by several weeks. Other mucous membranes including nasal, vaginal, and the vermilion border of the lips, may also be involved. Pruritus is not a common feature of pemphigus.

Other clinical features

P.V. generally occurs during the fourth and fifth decades of life, but may occur in all age groups including children. A genetic link has been suggested but certainly not proved by increased frequency of the leucocyte antigen HLA-AI3 in these patients.

Investigations

1. Biopsy – histopathology: P.V. is characterrzed histopathologically by suprabasal intraepidermal bulla formation with loss of cohesion of the epidermal cells. This latter finding, a process called acantholysis, is a histopathologic hallmark of this disease.
2. A Tzanck preparation is a useful screening cytologic procedure for the identification of acantholytic cells.
3. Direct immunofluorescence of adjacent normal skin shows intercellular epidermal deposits of IgG and C3.
4. Indirect immunofluorescence or enzyme-linked immunosorbent assays (ELISA) can also be used to confirm the diagnosis - the serum from a patient with pemphigus contains antibodies that bind to the desmogleins(I, III) and plakoglobin in the desmosomes of normal epidermis. The titre of these antibodies correlates loosely with clinical activity and may guide changes in the dosage of systemic steroids.

PEMPHIGUS VEGETANT

A rare variant of p.vulgar. Disease occurs in patients with intact immune system. Two types of P.vegetant have been recognized: a Neumann type whose and prognosisc losely resemble P .vegetant, and Hallopeau type which has been considered a less severe form of the disease.In the early stages of the disease, the lesions of p. vegetant are identical to those of p. vulgar. Flaccid weeping bullae predominate, but in the healing stages hypertrophic vemrcoid granulation arise from denuded areas left by ruptured bullae. Gradually the lesions may become hyperkeratotic and papillomatous, especially in the intertriginous areas. As in p.vulgar oral lesions occur frequently and are often the presenting symptomatology of p.vegetant. The vermilion border of the lips is a common site of involvement, and other mucosal surfaces may be involved as well.

Histopathology: P.vegetant is also characterized by deep, suprabasal acantholytic bulla formation, especially in early lesions. Later lesions may demonstrate pseudoepitheliomatous hyperplasia, hiperkeratosis, and papillomatosis in addition to acantholysis. Intraepidermal abscesses of eosinophils are frequently present and are considered a diagnostic hallmark of p.vegetant.

PEMPHIGUS FOLIACEUS

Bullous lesions may be entirely absent and, when present, are found only in early stages of the disease.

They may arise on erythematous bases, less frequently on normal-appearing skin. In addition to small bullae, patients often describe a slowly spreading eczematoid patch as the initial cutaneous manifestation. Shallow erosions, scales and crusting are the prominent clinical features of this form of the disease. In contrast o pemphigus vulgaris, oral lesions are not frequently present. Severe pruritus may cause the patient considerable discomfort. Pemphigus foliaceus is also mediated by circulating

autoantiboides to a 160-kDa intercellular antigen, desmoglein I, in the desmosomes of keratinocytes.

PEMPHIGUS ERYTHEMATOSUS(SYNDROME SENEAR-USHER)

Characterized clinically by an erythematous lupus-like rash of the "butterfly area" of the face and by superficial bullous or scaling lesions elsewhere that have a seborrheic quality, the disease histologically is identical to pemphigus foliaceus. The disease has also been referred to as seborrheic pemphigus because of the superficial, seborrheic nature of the eruptions.

Course

The course of all forms of pemphigus is prolonged, even with treatment, and the mortality rate of pemphigus vulgaris is still at least 15%. Most patients have a terrible time with weight gain and other side-effects from systemic corticosteroids and from the lesions, which resist healing. About one-third of patients with pemphigus vulgaris will go into complete remission within 3 years. Superficial pemphigus is less severe. With modern treatments, mostpatients with pemphigus can live relatively normal lives, with occasional exacerbations.

Complications

Complications are inevitable with the high doses of steroids and immunosuppressive drugs that are needed to control the condition. Indeed, side-effects of treatment are now the leading cause of death. Infections of all types are common. The large areas of denudation may become infected and smelly, and severe oral ulcers make eating painful.

Differential diagnosis

Widespread erosions may suggest a pyoderma, impetigo, epidermolysis bullosa or ecthyma. Mouth ulcers can be mistaken for aphthae, Behcet's diseaseor a herpes simplex infection. Scalp erosions suggest bacterial or fungal infections.

Management

1. Glucocorticoids 2 to 3mg/kg of body weight of prednisone until cessation of new blister formation and disappearance of Nikolsky`s sign. The initial dose should be high enough (100 to 200 mg of prednisone per day) to completely suppress new blister formation. Further reduction must be gradual. Pemphigus antibody determination at weekly intervals, in addition to the clinical activity, may be helpful in gauging the prednisone doses as antibody titers often closely reflect disease activity.
2. Immunosupressive agents: Cyclophosphamid 100 to 200 mg daily, 2 to 3 weeks later. Azathioprine 2 to 3mg/kg of body weight until complete clearing; tapering of dose to 1mg/kg(3 to 4 weeks).
3. Intravenous gamma globulin (IVIG) may be useful in severe cases, especially paraneoplastic pemphigus.

4. Rituximab, an anti-CD20 antibody, was found to improve otherwise untreatable severe cases of Pemphigus vulgaris.
5. Plasmapheresis.

DERMATITIS HERPETIFORMIS (DUHRING-BROCQ DISEASE)

Definition: is chronic recurrent, intensely pruritic, subepidermal bullous disease.

Clinical features:

1. **Skin lesions:** early lesions are erythematous papules, urticarial weals or vesicles. After, on erythematous and edematousus plaques develop herpetiform grouped small bullae. The lesions are symmetrically distributed on the extensor surfaces. Areas of predilection are the elbows, forearms, knees, buttocks, shoulders, posterior nuchal zone, scalp, face, posterior axially fold, sacral region. The eruption is characteristically polymorphous. Burning stinging and itching habitually precede the location of a new lesion.
2. **Mucous lesions:** oral mucosa is rarely involved, also larynx.
3. **Other manifestations**
    a. A gluten-sensitive enteropathy with villous atrophy and malabsorbtion is present in the vast majority of patients. Clinically, significant celiac disease is rare. Gluten-sensitive enteropathy (sprue, adult celiac disease), demonstrable by small bowel biopsy, is always present, but most patients do not suffer from diarrhoea, constipation or malnutrition as the enteropathy is mild, patchy and involves only the proximal small intestine. A range of antibodies can be detected in serum, notably directed against tissue transglutaminase, reticulin, gliadin and endomysium – a component of smooth muscle. In a minority of patients with gluten-sensitive enteropathy, IgA antibodies against tissue transglutaminase cross-react with antigens of epidermal transglutaminase leading to granular deposits of IgA and then C3 in the superficial dermis under the basement membrane zone (Fig. 9.5). These induce a neutrophil-rich inflammation, which separates the epidermis from the dermis. The IgA deposits in skin clear slowly after the introduction of a gluten-free diet. There is a strong association with certain human leucocyte antigen (HLA) types, particularly HLA-DR3 and HLA-DQw2.
    b. Exacerbation of disease after halogen administration.
    c. Lymphoma involving the small bowel has been reported in isolated cases.
    d. Milk intolerance and protein-losing enteropathy, gastric achlorhydria and atrophic gastritis, splenic atrophy have been reported.
    e. Thyroid disorders are increased in incidence at the patients with dermatitis herpetiformis .
    f. An increased incidence of internal malignancy is also signaled in -patients with DH.

Laboratory findings:

1. Cytology (Tzanck preparation): epidermal cells are not present.
2. Histology: in early lesions the histology reveals edema, neutrophils, eosinophils, at the dermal-papillary tips and the formation of microabscesses. The epidermis separates and a subepidermal bulla formation result.
3. DIF of noninvolved skin reveals deposits of IgA alone or together with C3, arranged in a granular pattern in the dermal papillae. IgM and IgG deposits are occasionally detectedi n similar distribution. These deposits may be focal, more often seen in previously involved skin or in perilesional skin.
4. Immunoelectron microscopy detects IgA alone or in association with C3, IgG or IgM as clumps in the upper dermis.
5. IIF: anti-basement membrane autoantibodies are undetectable. IgA-containing immune complexes and autoantibodies to gliadin, reticulum and smooth muscle endomysium are noted in the sera.
6. HLA markers studies reveal at a higher frequency haplotypes HLA DR3, DQw2, 88, A1.
7. Jadassohn test :
    a. Cutaneous test (patch test) - On unlesioned area of skin apply with a spatula 50% potassium iodide ointment (forearm or between the shoulder blades). Cover with wax paper on top and secure with adhesive plaster for 24 or 48 hours. After 24 or 48 hours in contact with the ointment appears erythema and other morphological features that are typical of dermatitis Dühring (spots, papules, vesicles on erythematous base).
    b. Internal probe - Warn patient that may be exacerbation of the pathological process. Have a drink 1 tablespoon of 3% solution of potassium iodide 1-2 days to check the result of the test.

Pathophysiology

Several factors are incorporated in a potential Pathophysiology of the disease:

1. The high frequency of the HLA antigens DR3, DQw2, 88, A1.
2. The role of IgA immune complexes.
3. The relationship between this IgA autoimmune disorder and gluten-sensitive enteropathy.
4. The role of gastrointestinal disease in DH is evidenced by the resolution of both the skin lesions and gut abnormalities in response to a gluten free diet.
5. Granular deposits of IgA are present in the skin of the patients with DH but not patients with isolated gluten-sensitive enteropathy. Whatever the mechanism involved in the deposition of IgA in the skin of the patients with DH, the most likely final common pathway for the development of the skin lesions may be the activation of the complement cascade via the alternative pathway, resulting neutrophil chemotaxis, release of enzymes, tissue destruction and the development of lesions characteristic of disease.

Differential diagnosis: bullous pemphigoid, linear IgA disease, pemphigus vulgaris, eczema, urticaria, erythema multiforme, prurigo et. aI.

Course

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

Complications

The complications of gluten-sensitive enteropathy bullous diseases include diarrhoea, abdominal pain, anaemia and, rarely, 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.

Treatment

1. Sulfones: dapsone orally, 100-200 mg/day; once a favorable response is attained, the maintenance dose of 25-50 mg/day for many years is necessary
2. Sulfaridine, orally, 0,5 g t.d.s., in patients who cannot tolerate dapsone.
3. Sulphamethoxypyridazyne orally 0,5-1 g/day may also be used.
4. Colchicines.
5. Tetracycline and nicotinamide.
6. Gluten-free diet.7. Elimination of halogens.

ICHTHYOSIS VULGARIS

Cause

Inherited as an autosomal dominant disorder, this condition is common and affects about 1 person in 300. The relevant gene may be concerned with the production of profilaggrin, a precursor of filaggrin, itself a component of keratohyalin granules.

Presentation

The dryness is usually mild and symptoms are few. The scales are small and branny, being most obvious on the limbs and least obvious in the major flexures. The skin creases of the palm may be accentuated. Keratosis pilaris is often present on the limbs.

Clinical course

The skin changes are not usually present at birth but develop over the first few years of life. Some patients improve in adult life, particularly during warm weather, but the condition seldom clears completely.

Complications

The already dry skin chaps in the winter and is easily irritated by degreasing agents. This should be taken into account in the choice of a career. Ichthyosis of this type is apt to appear in a stubborn combination with atopic eczema.

Differential diagnosis - It can usually be distinguished from less common types of ichthyosis on the basis of the pattern of inheritance and of the type and distribution of the scaling.

Investigations: Histologic Findings - The histological appearance of both hereditary ichthyosis and acquired ichthyosis is practically identical. The stratum corneum shows compact hyperkeratosis, although some areas can be laminated. Follicular plugging may be present and represents associated keratosis pilaris. The granular layer is usually one-layer thick or absent.

Treatment The mainstay of symptomatic management is reduction of scaling through the continual use of lubricants and emollients. A recently introduced ceramide-containing lipid cream has proved to be effective. Preparations containing urea and keratolytics, such as α-hydroxy, lactic and salicylic acid are beneficial, although care must be exercised to prevent salicylate toxicity. Topical retinoids may be valuable but can cause skin irritation. Vitamin D analogues seem ineffective. Systemic treatment with acitretin or isotretinoin is possible but rarely necessary. The use of moisturizing cleansers and humidifiers may be helpful.

EPIDERMOLYSIS BULLOSA(also known as the mechanobullous disorders)

Epidermolysis bullosa is a term given to three major groups and approximately 16 variants of rare dominant and recessive genetic diseases in which minor trauma cases non-inflammatory blistering.

The pathogeness is unknown. These diseases are classified as scarring or non-scarring and histologically by the level of blister formation.

Classification:

- Simplex: blistering at basal cell level or above
- Junctional: blistering at the lamina lucida level
- Dystrophic: blistering below the lamina densa level

EPIDERMOLYSIS BULLOSA SIMPLEX- KOEBNER VARIANT

Most are inherited as autosomal dominant conditions and are caused by abnormalities in genes responsible for production of the paired keratins (K5 and K14) expressed in basal keratinocytes. Linkage studies show that the genetic defects responsible for the most common types of simple epidermolysis bullosa lie on chromosomes 17 and 12.

Aggravating factors:

- Warm weather
- Accompanying hyperhydrosis of feet is common
- Secondary bacterial infections common

Blisters form within or just above the basal cell layers of the epidermis and so tend to heal without scarring. Involvement of nails and mucosae is frequent but subtle. The problems are made worse by sweating and ill-fitting shoes.

Cutaneous findings:

- Onset at birth or within the first few weeks of life
- Congenital lesions may heal with scarring, lesions after birth heal without scarring
- Distribution is generalized but acral areas are most frequently affected, flexor sites may be involved especially in warrner weather
- Mild to moderate hyperkeratosis of soles is common
- Often improvement at puberty especially in women

Extra-cutaneous finding

- Teeth are normal
- Nails may show transient mild involvement
- Oral and nasopharyngeal mucosa involvement is mild to moderateand usually decreases with age
- Occasional eye abnormalities, including myopia magna

Pathologic findings

- Basal cell cytolysis, minimal to mild dyskeratosis
- Tonofilament clumping at EM level

Other forms

- **Weber-Cockayne**
- *Dowling-Meara variant (Herpetiformis)*
- *Mottled hyperpigmentation*
- *Kallin syndrome*
- *Ogna variant*
- *Bart variant*
- *Mendes de Costa variant*
- *Letalis variant*
- *Superficialis*

Management

Blistering can be minimized by avoiding trauma, wearing soft well-fitting shoes and using foot powder. Large blisters should be pricked with a sterile needle and dressed. Their roofs should not be removed. Local antibiotics may be needed.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

There are many subtypes, all of which probably result from abnormalities of collagen VII, the major structural component of anchoring fibrils.

1. **Autosomal dominant dystrophic epidermolysis bullosa -** In this type blisters appear in late infancy. They are most common on friction sites (e.g. the knees, elbows and fingers), healing with scarring and milia formation. The nails may be deformed or even lost. The mouth is not affected. The only treatment is to avoid trauma and to dress the blistered areas.
2. **Autosomal recessive dystrophic epidermolysis bullosa -** In this tragic form of epidermolysis bullosa, blisters start in infancy. They are

subepidermal and may be filled with blood. They heal with scarring, which can be so severe that the nails are lost and webs form between the digits. The hands and feet may become useless balls, having lost all fingers and toes. The teeth, mouth and upper part of the oesophagus are all affected; oesophageal strictures may form. Squamous cell carcinomas of the skin are a late complication.

Extracutaneous involvement

- Oral mucosal involvement is generally mild, but occasionally includes esophageal stenosis
- Teeth are normal or mildly dystrophic
- Keratitis may occur

Pathologic findings

- Blistering beneath the basement membrane
- Anchoring fibrils may be decreased in number and poorly developed

Other forms

- Dystrophic EB – minimus
- Pretibial
- Albopapuloidea(Pasini variant)
- Hallopeau- Siemens(Gravis)
- Inversa
- Transient bullous dermolysis of the newborn

Diagnosis (for both forms).

Electron microscopic examination of the skin is the standard for diagnosis. Immunofluorescence tests for localization of type IV collagen, laminin, and pemphigoid antibodies in the roof or floor of bullae help differentiate the forms of EB.

Management.

It is especially important to minimize trauma, maintain nutrition, prevent contractures and web formation between the digits, and combat anaemia and secondary infection. Dilantin, a known collagenase inhibitor, is not an effective treatment for recessive dystrophic EB. Phenytoin, which reduces the raised dermal collagenase levels found in this variant, and systemic steroids are disappointing. Genetic counseling is essential, and fetal skin biopsy techniques have been developed for prenatal diagnosis.