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TRUE PEMPHIGUS: PATHOGENESIS, DIAGNOSIS, TREATMENT

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Annotation: True pemphigus (PV) is an autoimmune disease of the skin and mucous membranes, which is histologically characterized by intraepidermal blisters resulting from acantholysis . The name "pemphigus" ("pemphigus") was first used by Hippocrates (460 - ca. 370 BC) to designate a severe fever accompanied by the appearance of blisters on the skin.In the general structure of skin diseases, the share of this disease ranges from 0.7 to 1%. Women aged 40 to 60 years are most often affected.

At present, the autoimmune nature of the disease is beyond doubt. It is known that the antigen of pemphigus foliaceus is desmoglein 1 (a transmembrane glycoprotein with a molecular weight of 150 kDa), and the antigen of pemphigus vulgaris is desmoglein 3 (a glycoprotein with a molecular weight of 130 kDa).Both antigens are present only on stratified squamous epithelial cells and are components of desmosomes. The density of desmogleins 1 and 3 in the layers of the epidermis is different. Desmoglein 3 is present predominantly in the lower layers of the epidermis; as one moves to the surface layers, its amount noticeably decreases. Desmoglein 1 is found predominantly in the upper layers of the epidermis.There is a difference in the distribution of desmogleins in the epidermis depending on the part of the body. Desmoglein 1 is maximally represented in the epidermis of the upper half of the body and face, and desmoglein 3 is maximally represented in the epidermis of the scalp and oral mucosa , which determines the clinical picture of various forms of IP.

The pathogenesis of pemphigus vulgaris is not completely clear. The disease has long been viewed as a humoral disorder in which clinical manifestations are the result of the action of autoantibodies directed against desmosomal antigens.

The pathogenesis of a large number of autoimmune diseases is based on the genetic characteristics of the immune system.The exclusive role of molecules of the major histocompatibility complex (MHC) is to implement the immune response from its beginning (antigen recognition) to the final stage (destruction of an object carrying foreign information). As is known, the T-cell receptor recognizes a foreign object if it is represented by MHC class II molecules. Violation of this mechanism leads to the development of pathological processes in the human body.Currently, most researchers consider the presence of HLA-DR4 (DRB1*0402) and DRw14 (DRB1*1401) in an unstable relationship with DQB1*0503 to be a factor predisposing to the onset of the disease . Apparently, the presence of these alleles determines the presence of desmoglein-specific autoreactive CD4+ cells in the body. In healthy carriers of these alleles, only desmoglein-specific CD4+ cells of the ^-phenotype are detected in the blood; when cells with the ^2 phenotype appear, the disease develops.

Clinically, pemphigus vulgaris, foliaceus, erythematous, vegetative, and Brazilian pemphigus (endemic type) are distinguished.

Recently, a division has been proposed taking into account IP antigens:

A. Pemphigus vulgaris.
B. • Pemphigus vegetans (local form of vulgaris).
C. B. Pemphigus foliaceus.
D. • Erythematous pemphigus (local foliate form).
• Brazilian pemphigus (endemic foliaceous form).

Pemphigus vulgaris is the most common. Clinically, it is characterized by the appearance of blisters, usually with a flabby covering, on apparently intact skin and on hyperemic areas of the skin or on the oral mucosa. The size of the bubbles ranges in size from a lentil to the palm of an adult. The contents of the bubbles are initially transparent, then become cloudy.

With further flow, erosions are formed in place of the bubbles with fragments of bubble covers along the periphery or crusts, under which there is an erosive surface. Erosions tend to grow peripherally.Mild trauma to the epithelium is usually observed - Nikolsky's symptom:

1. Marginal - if you pull a piece of the stratum corneum, the stratum corneum peels off over a considerable distance.
2. From clinically unaffected skin - if you rub the surface of the skin covered with normal-looking epidermis, the stratum corneum is easily removed.The patient's clothes dry out to the erosions, which restricts the patient's movements. Even with a slight movement, the skin stuck to clothing comes off, causing severe pain.Lesions localized on the oral mucosa and on the red border of the lips are especially painful.The lips are covered with serous-hemorrhagic crusts, under which there is an intense red weeping surface. It is usually not possible to detect blisters on the oral mucosa; the pathological process, as a rule, is represented by erosions, often covered with a grayish coating. It is difficult for the patient to open his mouth, eating is extremely difficult and is accompanied by severe pain, and there is a pronounced bad breath.

Pemphigus vegetans is also characterized by the appearance of blisters on the skin and mucous membranes, with a predominant localization in the area of skin folds (axillary, inguinal, under the mammary glands). The blisters usually open quickly, and papillomatous growths appear on the surface of the resulting erosions. Pemphigus foliaceus is characterized by the fact that the blisters that appear on the surface of the skin have a very thin covering and the exudate usually ruptures it. The exfoliated areas of the epidermis remain in their original place, and the exudate from below raises new layers of the epidermis. Thus, the epidermis forms layers, which was the reason for giving this type of pemphigus the name "foliate".Erythematous pemphigus in its course is considered a relatively benign form of the disease. It begins with the formation of butterfly-shaped erythematous lesions on the skin of the face, which resembles the clinical picture of erythematosis. The affected areas are covered with yellowish scaly crusts with an eroded surface exposed underneath.

Without treatment, 75% of patients die within a year. The painful process lasts for weeks or months. Patients lose weight, lose sleep and appetite. When pemphigus generalizes, death occurs within a short time. When diagnosing IP, the totality of the results of clinical, cytological, histological and immunofluorescent examination is taken into account. Detection of acantholytic cells (Tzanck cells) in fingerprint smears from erosions and blisters is the fastest and most accessible test, but its information content is low, and you should not rely on this method alone.It is undeniable that a qualified diagnosis of IP is impossible without an immunofluorescence study.In the indirect immunofluorescence reaction, antibodies against the components of the epidermis circulating in the patient's peripheral blood are detected. Using a direct immunofluorescence reaction, antibodies localized in the intercellular spaces of the epidermis are detected. The only treatment for this disease that has a morbistatic effect is the prescription of corticosteroid drugs.

However, such therapy is not specific, and to achieve remission, high doses of corticosteroids (CS) are required, which creates a risk of serious side effects: steroid diabetes, osteoporosis, myocardial infarction, arterial hypertension, arrhythmia, pancreatitis, gastric ulcers , Cushing's syndrome, etc. Most patients die from complications arising during treatment.

Systemic CS therapy is the most studied method of treating PV. Its use since the early 1950s has sharply reduced mortality from 75 to 30%; currently it does not exceed 10%. Clinical recovery can be achieved fairly quickly after initiation of CS therapy. On average, the cessation of blistering is observed after 2-3 weeks, and complete healing is observed after 6-8 weeks.

As a rule, high doses of CS (prednisolone, methylprednisolone, triamcinolone) are prescribed - 60-120

mg/day in terms of prednisolone. The patient receives the indicated dose until all erosive surfaces are completely epithelized, then a slow reduction is made to a maintenance dose of 10-15 mg/day. The patient takes a maintenance dose for many years, and often for life. When treating persistent, treatment-resistant cases of pemphigus, pulse therapy with CS is sometimes used. As a rule, methylprednisolone is used at a dose of 1 g/day IV for 5 days. In combination with large doses of CS, it is necessary to prescribe potassium, calcium, and anabolic steroids.

Adjuvant therapy for pemphigus is aimed at reducing the need for CS and, therefore, reducing side effects.

Immunosuppressive drugs such as methotrexate, cyclosporine A, azathioprine, cyclophosphamide, mycophenolate mofetil suppress the immune response. However, they do not cause a decrease in immunoglobulin serological titers, as would be expected if they suppressed antibody synthesis. Because these drugs have multiple effects on cell function, their potential benefits may be due to nonimmune mechanisms. The methods of using these drugs for pemphigus are different - from oral to intravenous administration, from administration at the beginning of treatment to suppress the activity of the process to the use of CS instead of a maintenance dose. Methotrexate is prescribed at a dose of 25 mg IM 1 time per week, for a course of 3-5 injections, azathioprine - at a dose of 1.5-2 mg/kg/day in 2 doses.

Cyclosporine A in the complex therapy of pemphigus is prescribed at a dose of 3-5 mg/kg after complete epithelization of all erosive surfaces; the daily dose of the drug is reduced to a maintenance dose, recommended for 2-4 months.

All authors who used immunosuppressive therapy as adjuvant agree that such therapy contributes to more effective suppression of the pathological process. It also allows patients to be given a smaller total dose of CS and thereby reduce the risk of side effects. However, immunosuppressive drugs themselves can cause severe side effects, such as myelosuppression, anemia, hepatotoxic reactions, hemorrhagic cystitis, and renal dysfunction, so careful monitoring of blood and urine tests is necessary.Plasmapheresis is most often used among procedures that have an immunomodulatory effect in the complex treatment of IP. Plasmapheresis is, at first glance, an attractive procedure, because it is intended to remove circulating autoantibodies from the bloodstream, which are the cause of pemphigus.

However, according to a feedback mechanism, the level of antibodies in the bloodstream is regulated; the initial drop in the level of antibodies subsequently causes increased synthesis of new ones. Thus, the effectiveness of plasmapheresis depends on the balance between the amount of antibodies removed and newly produced. This equilibrium depends on the amount of plasma removed and the steps taken to prevent the synthesis of new antibodies. Plasmapheresis appears to be worth considering in patients with severe pemphigus refractory to standard therapy. Its value in the treatment of uncomplicated forms of pemphigus is questionable. Recently, a new method of adjuvant therapy for pemphigus has been proposed, which consists of the use of extracorporeal photochemotherapy (syn. photopheresis).

Extracorporeal photochemotherapy is used in the treatment of autoimmune and oncological diseases, as well as in transplant rejection. The method consists of combining leukapheresis with irradiation of lymphocytes pre-sensitized with 8-methoxypsoralen with ultraviolet A light.

It is assumed that methoxypsoralen, when activated by UV radiation, covalently binds pyrimidine bases of DNA and some molecules of the cell membrane. Cells affected by this effect are not capable of reproduction and must be removed from the bloodstream. This treatment method has proven itself well in cases of severe IP, as well as in cases of disease resistance to treatment with CS and immunosuppressive drugs.

Recently, there have been reports of the successful use of anti-L20 monoclonal antibodies (rituximab) in patients with severe pemphigus resistant to standard therapy.

It is believed that the ability of rituximab to eliminate B cells is realized through several mechanisms, including complement-dependent and antibody-dependent cellular cytotoxicity, as well as induction of apoptosis.

Timely diagnosis of IP, systemic corticosteroid therapy adequate to the severity of the disease, and well-chosen adjuvant therapy are the key to successful treatment, a favorable prognosis and long life for the patient.

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