CLINICAL CASE OF DIFUSED FORM OF PEMPHIGUS VULGARIS IN A SICK FEMALE AT AN ELDERLY AGE

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Annotation: The development of pemphigus in a 65-years old woman with obliterated onset of the disease, possibly, proved to be the cause of the late diagnostics, and resulted into untimely initiated therapy. Positive result was achieved after the correct interpretation of clinical and morphological findings and complex therapy.

Keywords: vulgaris pemphigus, acantholysis, Tzank cells, acantholytic cells.

Аннотация: Развитие пузырчатки у женщины в возрасте 65 лет со стертым дебютом заболевания, возможно, и явилось причиной поздней диагностики, а следовательно, несвоевременно начатой терапии. После правильной интерпретации клинических и морфологических данных и проведенной комплексной терапии удалось добиться положительного результата.

Ключевые слова: вульгарная пузырчатка, акантолизис, клетки Цанка, акантолитические клетки.

Pemphigus vulgaris is one of the most serious diseases. It constitutes 0.7 - 1% of all dermatological diseases [1, 4]. According to Andijan regional dermatovenerologic dispensary in the city of Andijan for 2020, 15 patients with pemphigus were treated at the in-patient department. Pemphigus can occur at any age. Most often, women get sick after 50 years; in recent years, cases in young people 18 - 35 years old have become more frequent. The most severe course is observed at the age of 30 - 45 years [1, 4]. Pemphigus (acantholytic, or intrinsic pemphigus) is an autoimmune disease characterized by the appearance of intra-epidermal blisters on visibly unchanged skin or mucous membranes. Appearance of suprabasal vesicles with acantholysis proved to be characteristic morphological basis [4, 8, 9]. The etiology of pemphigusis still remained unknown [1]. At present, the role of autoimmune processes, that develop in response to changes in the antigenic structure of epidermal cells under the influence of various damaging agents,is recognized as the leading one. Cell damage is possible as a result of chemical, physical, biological factors [4]. It was stated that in case of pemphigus, autoantibodies act against keratinocytes, the surface structures of epidermal cells.

Combination of autoantibodies (pemphigus - IgG) with glycoproteins of cell membranes (pemphigus - antigens) of keratinocytes leads to acantholysis, impairment of adhesion between

cells and the formation of blisters. It has been demonstrated that the complement system and inflammatory cells are not involved in this process, although the presence of complement increases the pathogenicity of autoantibodies, and infection at the sites of skin damage leads to the addition of an inflammatory process, what aggravates the patient's condition [7].

Various exogenous and endogenous factors, including genetic predisposition, may be the risk factors for the development of vulgaris pemphigus. It has been revealed that the HLA-DR and HLA-DQ polymorphism proved to be the basis of the genetic predisposition to pemphigus and other autoimmune diseases [4, 7].

The four clinical forms of vulgaris pemphigus have been differentiated: vulgar (ordinary), vegetative, leaf-shaped and erythematous (seborrheic). All clinical forms are characterized by a long chronic undulating course, leading, if remains untreated, to a violation of the general condition of patients. The most common pemphigus vulgaris constitutes up to 80% of all cases [4].

The disease begins with lesions of the mucous membranes of the mouth and throat in more than 50% ofcases. At first, single or few in number, small flabby blisters with serous contents,appearing on unchanged mucous membranes, can be located in any area. Their number gradually increases. Within 1-2 days blisters quickly burst, forming weeping painful erosion with a bright red bottom or covered with a whitish bloom of erosion, bordered along the periphery by scraps of whitish epithelium. While progressing, the erosions become numerous, increasing in size and merging with each other form festoon-shaped foci.

Patients experience pain when eating, talking, and swallowing saliva. Its characteristic features are hyper - salivation and a specific putrid smellin the mouth. The voice may be hoarse when the larynx and pharynx are affected. For a long time, patients are observed by dentists or ENT doctors for stomatitis, gingivitis, rhinitis, laryngitis, etc. The lesion of the mucous membranes can remain isolated during several days up to 3-6 months and longer, and then the skin of the trunk, limbs and scalp becomes involved in the process.

The lesion of the skin begins with the appearance of single blisters, and then their number increases. Blisters are located on an unchanged skin surfaces, and more seldom in case of erythematous condition. Blisters are small in size, they have serous contents withtense covers. After a few days, some blisters on the skin dry up into yellowish crusts, or if the cover ruptures, bright red erosion can be exposed, discharging thick exudate. Erosions at this stage of the disease are not painful and proved to be quickly epithelialized. The general condition of the patients remains satisfactory. Regressed rashesare replaced bynewones.

This initial phase can last from 2 - 3 weeks to several months or even years. Then the generalization of the process, characterized by the rapid spread of the rash over the skin, and the extension to the mucous membranes of the oral cavity and genitals, if they had not been previously affected, occurs. As a result of eccentric growth, blisters increase in size due to exfoliation of the upper layers of the epidermis, the covers become flabby, and the contents become opaque or purulent. Under the weight of exudate, large blisters can take a pear-shaped form (N.D.Sheklakov's"pear syndrome"). Blisters then spontaneously burst with the formation of extensive erosional areas of the skin.

In case of pemphigus vulgaris, erosion is usually bright pink in color with a shiny wet surface. Tendency to peripheral growth with possible generalization of the skin process, formation of extensive lesions, deterioration of the general condition, addition of a secondary infection, development of intoxication proved to be the features of erosions; and if condition remains untreated, a fatal outcomes are possible [1-5].

Detachment of the externally unchanged epidermis when pressed on its surface near the blister or even on apparently healthy skin far from the lesion is an important diagnostic sign of pemphigus vulgaris (Nikolsky's symptom) [1]. There are three versions of Nikolsky's symptom, which allows assessing the extension of acantholysis. In the first case, when pulling the cover of a burst blister, the epidermis exfoliates beyond its borders. In the second option, the upper layer of the epidermis exfoliates, and if healthy skin is scrubbed between two blisters, an erosive surface is formed.

The occurrence of erosion after scrubbing healthy skin in a place without bullous elements indicates the presence of the third version of Nikolsky's symptom [5]. One of the modifications of Nikolsky's symptom is the Asbo-Hansen phenomenon: pressure with a finger on the cover of an unbursted blister increases its area due to further stratification of the acantholytic epidermis with vesicular fluid. Nikolsky's symptom is not always detected in the initial phase of pemphigus vulgaris, and only in the form of a marginal one. When the process is generalized, it is positive in all patients in all modifications [3].

Diagnosis of vulgaris pemphigusis basec ont recombination of theresults of clinical, cytological, histological and immunological examination. Clinical picture of the disease, the presence of a positive Nikolskys symptom and its modification, the phenomenon of "pear" described by N.D. Sheklakov, based on the phenomenon of acantholysis should be taken into consideration. Cytological examination reveals acantholytic cells (Tzank cells) in smears - prints from erosions and blisters after staining by the Romanovsky-Giemsa method (Tzank test).The

presence of Tzank cells in the bllisters is not pathognomonic, but it proved to be a very important diagnostic sign of the disease.

Histological examination allows revealing intra-epidermal location of fissures and blisters [1, 4]. The usage of immunofluorescence examination proved to be the required condition for qualified diagnostics of intrinsic pemphigus. By means of indirect immunofluorescence, antibodies against components of the epidermis are detected with the help of luminescent anti - IgG - human serum. IgG antibodies localized in the intercellular spaces of the thorn-like layer of the epidermis are detected by means of direct immunofluorescence in skin sections [1]. Laboratory data (anemia, leukocytosis, increased ESR, proteinuria, hypoalbuminemia, decreased sodium excretion in the urine, etc.), allowing to assess the severity of the process play a certain auxiliary role[3].Differential diagnosticsof Lever's bullous pemphigoid, Duhring's herpetiformis dermatitis, chronic benign familial pemphigus Guzhero - Haley - Haley, lupus erythematosus, seborrheic dermatitis, Lyell's syndrome, chronic vegetative pyodermais carried out [4].The treatment of vulgaris pemphigus proved to be quite complicated. Since the main chains of pathogenesis are interpreted from the position of autoimmune pathology, all existing therapeutic measures are carried out in the form of immunosuppressive effects on autoallergic processes through the use of corticosteroid and cytostatic drugs [1].

The treatment of pemphigus with corticosteroids has decreased death rate among patients from 90 to 10% [7]. Pemphigus is one of the diseases when corticosteroids are administered for health reasons, and the existing contraindications in these cases become relative. Positive eeffect of glucocorticoids is explained primarily by the blockage of main stages of biosynthesis of nucleic acids and proteins, standstill of the afferent phase of immunogenesis, decrease of lymphoid organs, destruction of medium and small thymic lymphocytes, inhibition of the formation of immune complexes.It is considered that corticosteroids exercise stabilizing effect on lysosomal membranes and inhibit synthesis of autoantibodies [1]. Thehighest doses of glucocorticosteroids are prescribed (from 60 - 100 to 150 - 300 mg / day of prednisolone) in case of severe pemphigus vulgaris and pemphigus foliaceous [1,4]. The dose of prednisolone is administered taking into account the extension of rashes and the severity of the disease. It shouldn’t be at less than 1 mg / kg / day. The daily dose is administered in such a way that 2/3 should be taken in the early morning hours (preferably after meals), and 1/3 - in the afternoon (12-13 hours).In a particularly severe condition of the patient, higher doses of prednisolone are prescribed - up to 300 mg / day [4]. At high doses, prednisolone can be partially replaced by parenteral administration or betamethasone preparation (prolonged forms can be used once every 7 - 10 days). Prolonged usage of corticosteroid drugs leads to the development of serious

complications and side effects; their rapid cancel causes the so-called cancel syndrome, and the disease recurs. Therefore, it is very important to carry out correction and prevention of side effects caused by prolonged usage of glucocorticosteroids. For prevention cancel syndrome, it is recommended to stop taking drugs or reduce their daily dose carefully and gradually. Initially, after achievement of a marked therapeutic effect (cessation of the appearance of new blisters, active epithelialization of erosions), which usually occurs after 2 - 3, sometimes after 4 weeks, a decrease in the dosage of glucocorticosteroids is possible on ¼ - 1/3 of the maximum initial dose. Then the dose of prednisolone is gradually, slowly, over several months, reduced to sustainable.The daily dose of hormone is gradually reduced, approximately once in every 4 - 5 days, up to 2.5 - 5 mg of prednisolone until the minimum sustainable effective dose of corticosteroid is achieved; its introduction ensures the remission of the disease.

Further, it is advised to administerthe sustainable dose of corticosteroids alternately. However, periodically (every 4 - 6 months) it should be decreased on 2.5 mg prednisolone equivalent.

Thus, by reducing the sustainable dose, it is possible to administer the 3 - 4 times decreased amount of hormone, in comparison to the initial sustainable dose. The permissible minimum sustainable dose can vary from 2.5 to 30 mg/day. Usually, pemphigus patients receive glucocorticosteroids during their whole life, sometimes they can be stopped [1, 4].

The addition of second-line drugs to the main therapy is indicated to increase the effect of treatment, reduce the side effects of corticosteroids as well as to prevent relapses when they are gradually stopped. Adjuvant therapy includes azathioprine, methotrexate, cyclophosphamide, mycophenolatamofetil, intravenous immunoglobulin and dapsone [9]. The combined usage of cytostatic and immunosuppressive drugs with corticosteroids makes it possible to achieve good therapeutic results in a shorter time and with lower daily doses of corticosteroids.

Many drugs such as alkylating agents and antimetabolites have cytostatic properties. From alkylating drugs, cyclophosphamide is the most widely used in the treatment of pemphigus. This drug is capable to enter into alkylation reactions with certain groups of proteins and nucleic acids of the cell, inhibiting various enzyme systems and dramatically disrupting the vital activity of cells, mostly highly active and lymphoid ones.Antimetabolites, which include purine base antagonists (azathioprine) and folic acid antagonists (methotrexate), resemble natural cell metabolites in structure and, competing with them, impair intracellular metabolism. As the result,the accumulation of substances toxic to cells occurs, leading to the death of actively proliferating cells. Azathioprine is prescribed in the dosage of 1.5-2 mg / kg / day,2-4 times in combination with steroids. Methotrexate is administered intramuscularly 10 - 20 mg (with good

tolerance up to 25 - 30 mg) 1 time per week (for a course of 3 - 5 - 8 injections). Cyclophosphamide is administered orally 100-200 mg / day, the duration of therapy is determined individually. In the process of treatment, it is necessary to control general and biochemical blood tests and urine.

In case of insufficient therapeutic efficacy of glucocorticosteroids and the presence of contraindications to the usage of cytostatics, immunosuppressants are prescribed. Cyclosporin A for the treatment of patients with intrinsic pemphigus is used in combination with corticosteroid drugs, and the daily dose of corticosteroids is reduced up to 3-4 times and corresponds to 25-50 mg of prednisolone. The daily dose of cyclosporin-A in the complex therapy of patients with intrinsic pemphigus in the acute stage should not exceed 5 mg per 1 kg of the patient's body weight and averages 3 - 5 mg / kg / day. Clinical picture, severity and extension of the disease, patient's age, presence of concomitant diseasesare taken into consideration. The first 2 days cyclosporin-A is prescribed in half dose for the evaluation of tolerability of the drug; then the daily dosage is divided into 2 doses - in the morning and in the evening with an interval of 12 hours. The daily dose of cyclosporin-A is decreasing after intensive epithelialization of actual erosions. Usually, an intensive dose is taken on average for the period of 14 - 20 days, followed by a gradual decrease in the daily dose of the drug up to 2–2.5 mg per 1 kg of the patient's body weight. Complete cleansing of the skin should not be considered the ultimate goal of treatment. After achieving remission, the patient should continue to take the minimum effective sustaining dose of cyclosporin-A, which should be prescribed individually. In such adosage, the drug can be used for a prolongedperiod of time (2 - 4 months) as a sustaining therapy. At present, treatment with immunosuppressants is not accepted generally [1, 4]. Aniline dyes, corticosteroid ointments with an antibacterial or antimycotic componentsas well as aerosols are used topically [3]. Methods of extracorporeal detoxification (plasmapheresis) are successfully used for additional treatment of pemphigus [1,6].

Regardless of success of native and foreign researchers in clarifying the mechanisms of pathogenesis and improving methods of treating patients with intrinsic pemphigus, the problem of pemphigus remains actual and is linkedwith the severity of the disease, its incurability and potential mortality [1].

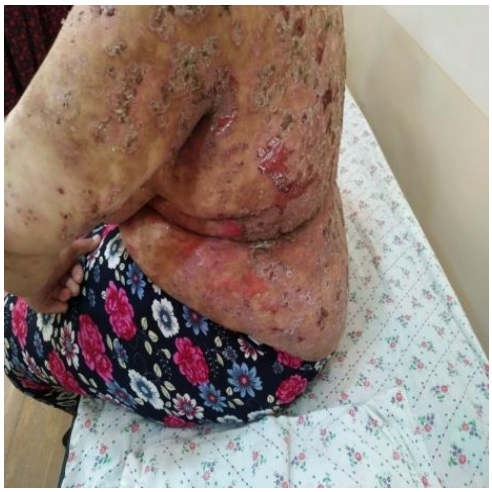
We have presented a clinical case demonstrating the difficulties of differential diagnosticsof “pemphigus”. Patient M.Yo., born in 1956, has been ill since the summer of 2019, when rashes on her scalp had been appearedfor the first time. She was treated independently, applied ointments with antibiotics without effect. In September 2020, the exacerbation of the skin process began. The rash hadbeen spread to the face and trunk. Within 2 weeks, the process

on the skin had been spread significantly: blister elements appeared on the chest, back and upper limbs.Serous-purulent discharge was noted on the scalpand the erosions took on a joint character.As the clinical picture was changed,the patient was admitted to the Skin Department of Dermatovenereology of Andijan State Medical Institute with a diagnosis of “pemphigus vulgaris”. According to the results of examinationin the 2nd skin department of Andijan Regional Dermatovenereologic Diseases Dispensary, this diagnosis was confirmed both clinically and laboratorial.It is known from the anamnesis that the patient had had a small focal myocardial infarction in 2015. She suffers from chronic bronchitis. Examination revealed anextended pathological process. Multiple erosions of bright red color with serous and serous-purulent discharge were scattered on her scalp, face, neck, trunk and upper extremities. Some erosion were covered with dense gray-yellow covers (Fig. 1 - 2). On the erythematous background, there were blisters of various size with a flabby covers and opaque contents. Nikolsky's symptom prove dtobe positive.

Laboratory examination of smears-prints from blisters on the forearms revealed single acantholytic cells in the preparation with coarse nuclei. Visible epithelial cells up to 8 - 10 – 12, with signs of atypia (enlarged coarse nuclei, binucleated cells) have been identified. Staphylococcus in the discharge from erosion was detected during bacteriological examination. According to the pathomorphological examination, the morphological picture of pemphigus was revealed; a blister with serous fluid and acantholytic cysts with purulent inflammation has been found in peripheral epidermis.In re-examination of the samplesin the oncological dispensary, the morphological picture of pemphigus was confirmed and no tumor growth has been found. A general clinical study showed an increase of ESR as well as a sharp positive C-reactive protein. Erosive antrum - gastritis, erosive-ulcerative bulbitis and duodenitis have been revealed in the process of fibrogastroduodenoscopy. Tiny (up to 0.2 cm) acute ulcers of the bulb and the upper-horizontal part of the bulb have been detected.

Taking into consideration the generalized process of skin lesions, parenteral administration of prednisolone in the dosageof 90 mg was prescribed with a gradual replacement to oral administration of this drug in the dosage of 30 mg. The patient has been undergone detoxification, antibacterial and antifungal systemic therapy and local treatment using antiseptics and anti-inflammatory drugs. Due to the presence of erosive gastritis, erosive-ulcerative bulbitis, as well as due to the intake of prednisolone, the patient was administered antisecretory therapy. Results of 3 weeks therapy demonstrated positive dynamics. Erosions have been completely epithelializedon the skin of the scalp, neck, chest, and back, covers have disintegrated. (Fig. 3). The patient was discharged for outpatient treatment with recommendations to reduce the dose of

prednisolone up to 1/4 tablet during 7-10 days under the control of a dermatovenerologist at a local polyclinic.



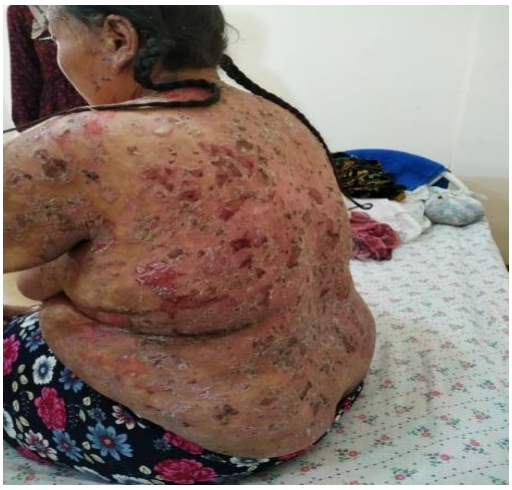


Photo (1-2) of the patient Y.M., 65 years old.

Diagnosis: Pemphigus vulgaris (before treatment)

The development of pemphigus in a 65-years old woman with obliterated onset of the disease, possibly, proved to be the cause of the late diagnostics, and resulted into untimely initiated therapy. Positive result was achieved after the correct interpretation of clinical and morphological findings and complex therapy.

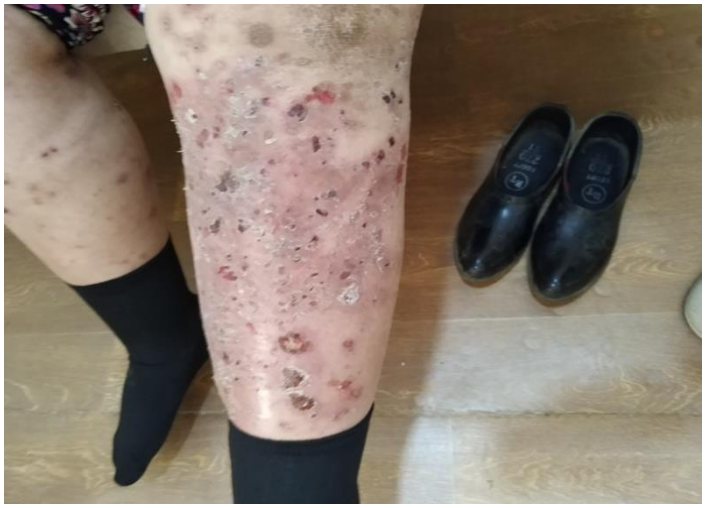


Photo (3) of the patient Y.M., 65 years old.

Diagnosis: Pemphigus vulgaris (after the treatment)

THE LITERATURE USED:

Used Books

1.Matushevskaya E.V. Pemphigus // Russian Medical Journal. 1997. No. 11.

2. Mordovtsev V.N., Mordovtseva V.V., Alchangyan L.V. Erosive and ulcerative skin lesions // Consilium Medicum. 2000. No. 5.

3. Paltsev M.A., Potekaev N.N., Kazantseva I.A., Kryazheva S.S. Clinical and morphological diagnostics and principles of treatment of skin diseases. A guide for doctors. Moscow: Medicine, 2010.

4. Kubanova A.A., Kisina V.I., Blatun L.A., Vavilov A.M. and others. Rational pharmacotherapy of skin diseases and sexually transmitted infections: A guide for practicing physicians / under the general. ed. A.A. Kubanova, V.I. Kissina. M .: Litterra, 2005. p. 882 (Rational pharmacotherapy: seria“A guide for practicing physicians”; v. 8).

5. Rubins A. Dermatovenereology. Illustrated guide. Moscow: Panfilov Publishing House, 2011, p. 368.

6. Application of plasmapheresis in patients with severe forms of chronic dermatoses. Dis ..., cand.med. sciences. Moscow. 1991.

7. SvirshevskayaE.V., MatushevskayaE.V. Immunopathogenesis and treatment of Pemphigus//Russian Medical Journal. 1998. № 6.

8. Kumar R., Jindal A., Kaur A., Gupta S. Therapeutic Plasma Exchange-A New Dawn in the Treatment of Pemphigus Vulgaris // Ind. J. Dermatol. 2015. Vol. 60 (4). P. 419.doi: 10.4103 / 0019-5154.160509.

9. Quaresma M. V., Bernardes-Filho F., Hezel J. et al. Dapsone in the treatment of pemphigus vulgaris: adverse effects and its importance as a corticosteroid sparing agent // An. Bras. Dermatol. 2015. Vol. 90 (3 Suppl. 1). R. 51–54.